

# **ABC of Sexually Transmitted Infections, Fifth Edition**

*Michael Adler, Frances Cowan, Patrick  
French, Helen Mitchell, John Richens*

**BMJ Books**

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Fifth Edition



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Michael Adler, Frances Cowan, Patrick French,  
Helen Mitchell, and John Richens

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Books

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# Preface

The first edition of this book appeared 20 years ago, virtually as a single author effort. This fifth edition comes at a time when the burden of sexually transmitted infections and HIV is at its greatest, yet and with an increasing importance of viral sexually acquired infections and new diagnostic tests. I am delighted that the fifth edition, and first of the new millennium, is now multi-author, written with colleagues from the Royal Free and University College. We have tried to capture recent advances at the same time as remaining practical with different approaches to control, diagnosis, and management depending on resources and facilities available.

Michael Adler,  
London 2004





# 1 Why sexually transmitted infections are important

Michael Adler

## What are sexually transmitted infections?

Sexually transmitted infections (STIs) are infections whose primary route of transmission is through sexual contact. STIs can be caused by mainly bacteria, viruses, or protozoa. In the developed world, viral diseases have become increasingly common and important, whereas bacterial STIs are more common in developing countries, but even this is changing with the increasing recognition of viral diseases.

The three most common presenting symptoms of an STI are urethral discharge, genital ulceration, and vaginal discharge with or without vulval irritation. The three most common STIs seen in clinics in the United Kingdom are genital warts, chlamydial infections, and gonococcal infections.

Trichomoniasis, pediculosis pubis, and genital herpes are common and are sexually transmitted. Scabies and vaginal candidiasis often are diagnosed in STI clinics, although they are not usually acquired sexually. Finally, sexually transmitted hepatitis (A, B, and C) and HIV are becoming more common.

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### Why STIs are important

- Common
  - Often asymptomatic
  - Major complications and sequelae
  - Expensive
  - Synergy with HIV
- 

---

### Sexually transmitted infections and associated presenting symptoms

	Urethral discharge	Vaginal discharge	Genital ulceration	Skin symptoms	Other
<b>Bacteria</b>					
<i>Chlamydia trachomatis</i>	++	+/-			
<i>Neisseria gonorrhoeae</i>	++	+/-			
<i>Treponema pallidum</i>			++	+	+
<i>Gardnerella vaginalis</i>	+/-	++			
<i>Haemophilus ducreyi</i>			++		
<i>Klebsiella granulomatis</i>			++		
<i>Shigella</i>					+
<b>Mycoplasmas</b>					
<i>Ureaplasma urealyticum</i>	+				
<i>Mycoplasma genitalium</i>	+	+			+
<b>Parasites</b>					
<i>Sarcoptes scabiei</i>				+	
<i>Phthirus pubis</i>				+	
<b>Viruses</b>					
Herpes simplex virus types 1 and 2	(+)	(+)	++		
Wart virus (papillomavirus)	(+)	(+)		+	+
Molluscum contagiosum (pox virus)				+	
Hepatitis A, B, and C					+
HIV				+	++
<b>Protozoa</b>					
<i>Entamoeba histolytica</i>					+
<i>Giardia lamblia</i>					+
<i>Trichomonas vaginalis</i>	(+)	++			
<b>Fungi</b>					
<i>Candida albicans</i>	(+)	++			

+ Common. - Less common

## The consequences

Sexually transmitted infections are a major public health problem and are one of the most common causes of illness, and even death, in the world today. They have far reaching health, social, and economic consequences, particularly in the developing world. The World Bank estimated that for women aged 15-44 years, STIs (excluding HIV) were the second most common cause of healthy life lost after maternal morbidity. Other studies have estimated that 5% of the total discounted healthy life years lost in sub-Saharan Africa are caused by STIs, excluding HIV, and that HIV alone accounts for 10% of healthy life years lost.

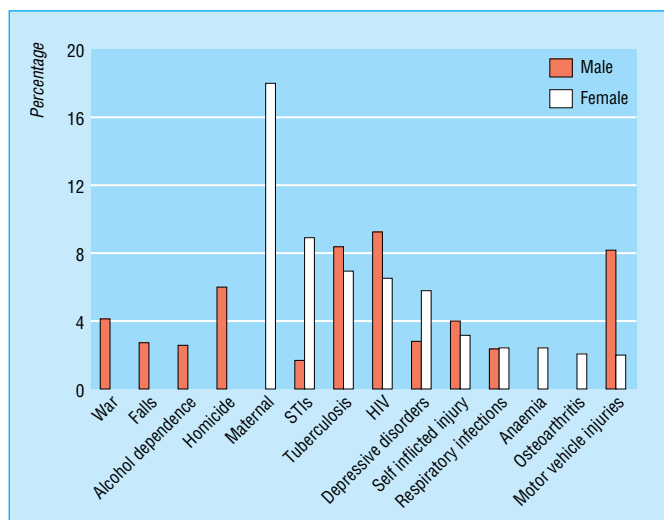
## Complications and cost

Most STIs are easy to diagnose and cheap to treat; however, viral conditions, such as herpes and HIV, are costly and incurable. Many infections remain unrecognised and undiagnosed, which results in considerable long term morbidity, which can be costly in human and monetary terms. The complications of untreated infections are far reaching, and include cancer, reproductive problems, and pregnancy related problems. Reproductive ill health (death and disability related to pregnancy and childbirth, STIs, HIV, AIDS, and reproductive cancers) has been calculated to account for 5-15% of the global burden of disease. Data on the monetary costs of the complications of STIs are sparse, particularly for the developing world. American data give estimates of total direct and indirect costs attributable to STIs to be \$9.9m annually, rising to \$16.6m if HIV and AIDS are included. In the United Kingdom only limited data are available. For example, the prevention of unplanned pregnancy by NHS contraception services probably saves over £2.5 billion per year, and the average lifetime treatment cost for an HIV positive person is between £135 000 and £180 000, with a monetary value of preventing a single onward transmission of somewhere between £0.5m to £1m in terms of individual health benefits and treatment costs. Finally, but not calculated accurately, dramatic cost savings can be made by preventing infertility.

Few economic data exist in the developing world in relation to the consequences of STIs, which are considerable and personally devastating. Many women become infertile without even realising that they have suffered from pelvic inflammatory disease. Estimates of the burden of infections for women in urban Africa have shown that chlamydial infection causes an average of 4.8 lost days of productive life and syphilis leads to 8.2 days per capita per year. Estimates suggest that with the high prevalence of syphilis in pregnant women, for example 10%, up to 8% of all pregnancies (beyond 12 weeks) would have an adverse outcome.

## Synergy between STIs and HIV

It is now recognised that there is a synergy between most STIs and HIV (particularly ulcerative and inflammatory conditions). Many research studies in both the developed and developing world have shown that HIV transmission and acquisition are enhanced by the presence of STIs, probably because of the inflammatory effect of STIs in the genital mucosa. HIV negative people with an ulcerative STI seem to be particularly vulnerable to infection, probably because in addition to the genital inflammation that occurs, ulceration causes physical disruption of the skin or mucous membrane, thus making it more permeable to infection. Non-ulcerative STIs also facilitate HIV acquisition and transmission but to a lesser degree. As they are



Top ten causes of healthy life lost in young adults aged 15-44 years

### Major sequelae of STIs

	Women	Men	Infants
Cancers	Cervical cancer Vulval cancer Vaginal cancer Anal cancer  Liver cancer  T cell leukaemia Kaposi's sarcoma	Penile cancer Anal cancer Liver cancer T cell leukaemia Kaposi's sarcoma	
Reproductive health problems	Pelvic inflammatory disease Infertility Ectopic pregnancy Spontaneous abortion	Epididymitis  Prostatitis Infertility	
Pregnancy related problems	Preterm delivery		Stillbirth  Low birth weight  Pneumonia Neonatal sepsis  Acute hepatitis Congenital abnormalities
Neurological problems	Neurosyphilis	Neurosyphilis	Cytomegalovirus Herpes simplex virus Syphilis associated neurological problems
Other common health consequences	Chronic liver disease  Cirrhosis	Chronic liver disease  Cirrhosis	Chronic liver disease  Cirrhosis

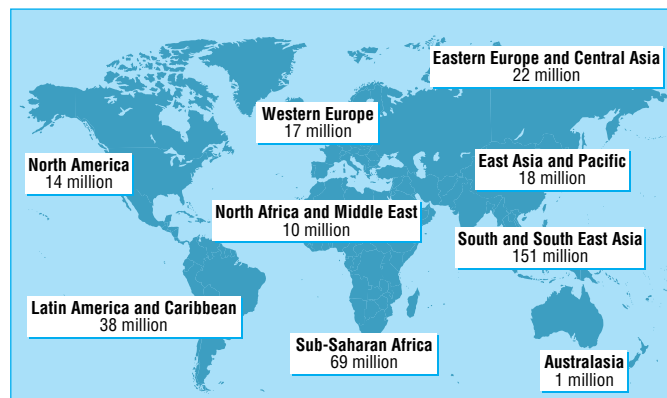
so common in many parts of the world, however, their impact on the HIV epidemic is likely to be considerable. HIV positive people with intercurrent ulcerative and non-ulcerative STIs have increased rates of genital shedding of HIV, which diminish when the STI is resolved. Clinical studies have shown that HIV positive patients with a urethral infection have an eightfold increase in HIV-1 RNA in semen, which falls after treatment. The likelihood of infection per exposure to HIV for any sexual contact is in the order of 0.1, which will increase considerably if an STI is present by the order of threefold to fivefold. This synergy, and a realisation that the control of STIs can have a profound effect on the incidence of HIV, has led to an increased drive and interest in STI control programmes.

## Size of the problem

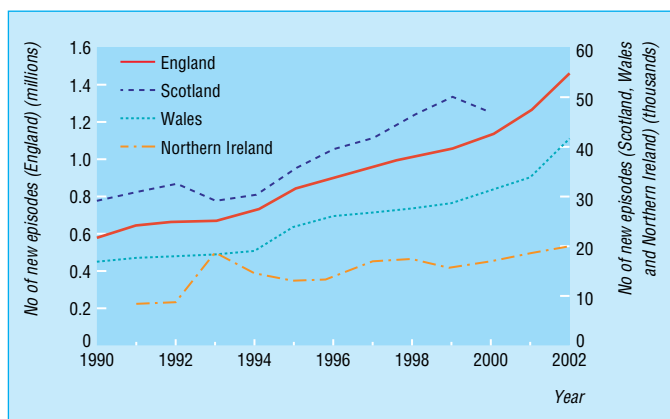
The size of the global burden of STIs is uncertain because of the lack of effective control and notification systems in many countries. The World Health Organization (WHO) has estimated a total of 340 million new cases of curable STIs in adults per annum, mainly in South and South East Asia (151 million new cases per year), and sub-Saharan Africa (69 million). In eastern Europe and Central Asia, the estimate is 22 million, and 17 million in western Europe. The prevalence and incidence per million of the population varies regionally, for example between sub-Saharan Africa and western Europe it is eightfold and fourfold, respectively.

### Role of STIs in the acquisition of HIV

- HIV acquisition increases by twofold to fivefold in the presence of other STIs
- Ulcers disrupt mucosal integrity and increase the presence or activation, or both, of HIV susceptible cells (for example, CD4 lymphocytes)
- Non-ulcerative STIs (such as gonorrhoea, chlamydia, *Trichomonas vaginalis*, and bacterial vaginosis) increase the presence or activation, or both, of HIV susceptible cells



Estimated new cases of curable STIs among adults (global total 340 million). Data source: World Health Organization



All diagnoses and workload at genitourinary medicine clinics by country, 1990-2002. Data are unavailable currently for Scotland for 2000-2 and Northern Ireland for 1990. Adapted from slide from Health Protection Agency ([www.hpa.org.uk](http://www.hpa.org.uk)), Communicable Disease Surveillance Centre. Data from KC60 statutory returns and ISD(D)5 data

The United Kingdom has a network of clinics dealing with STIs (departments of genitourinary medicine (GUM)), and such clinics have seen a very substantial increase in the number of attendances over the past decade. Such attendances have doubled, reaching 1.5 million in the year 2002. Even in the last seven years, increases of over 100% have been seen in cases of chlamydia, gonorrhoea, and syphilis.

### Gonorrhoea

To interpret differences between countries and even trends is difficult because of the variation in reporting practices and the provision of facilities. Rates of gonorrhoea vary between European countries. During the early to mid 1970s the number of cases of gonorrhoea peaked in most European countries. The subsequent advent of HIV and AIDS in the 1980s led to safer sexual practices and a reduction in the incidence of gonorrhoea, which has not been sustained in all countries. For example, between 1996 and 2002 an increase has been seen in both male and female cases of gonorrhoea in England

### New diagnoses of selected STIs in GUM clinics (England, Wales, and Northern Ireland, 2002)

	2002	% change 1996-2002
Chlamydia	81 680	139
Genital warts	69 417	17
Gonorrhoea	24 953	106
Genital herpes	18 392	16
Syphilis	1193	870

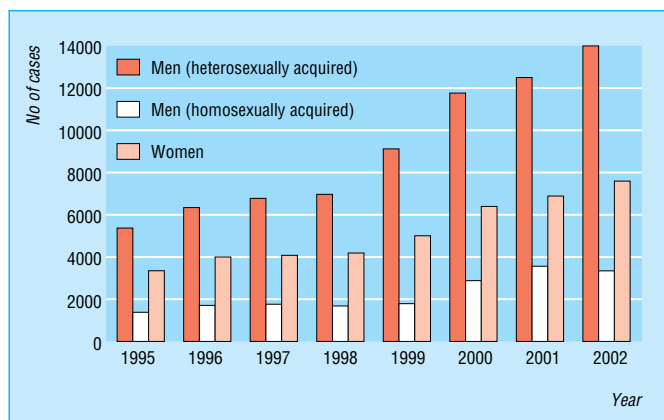
### Estimated prevalence and incidence of STIs by region

Region	Prevalence per million	Incidence per million
Sub-Saharan Africa	32	69
South and South East Asia	48	151
Latin America and Caribbean	18.5	38
Eastern Europe and Central Asia	6	22
North America	3	14
Australasia	0.3	1
Western Europe	4	17
Northern Africa and Middle East	3.5	10
East Asia and Pacific	6	18
<b>TOTAL</b>	<b>116.5</b>	<b>340</b>

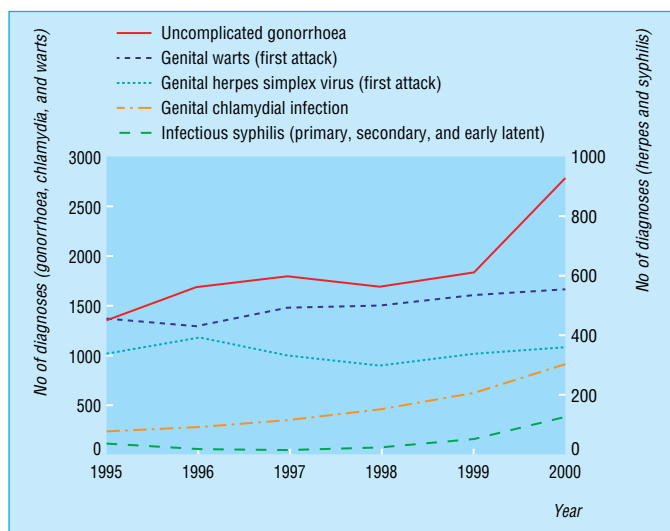
# ABC of Sexually Transmitted Infections

and Wales (114% increase in the number of cases in heterosexual men from 8051 to 17 260, and an 86% increase in cases in women from 4045 to 7542). The incidence of gonorrhoea has increased since 1996 in homosexual men, particularly in those living in London, as has that of other STIs. In 2002, 16% of gonorrhoea diagnoses in men, and 19% of those in London, were acquired through homosexual sex.

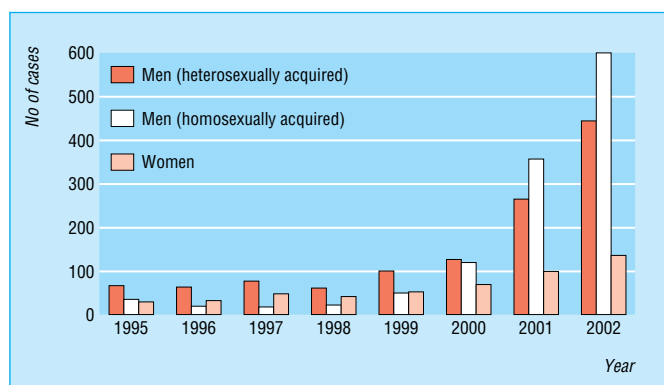
Other western European and Scandinavian countries have also seen recent increases, for example in France and Sweden. Eastern Europe, and particularly the newly independent states of the former Soviet Union, has seen an epidemic of STIs, with high rates of gonorrhoea in Estonia, Russia, and Belarus.



Cases of uncomplicated gonorrhoea seen in genitourinary medicine clinics by sex and male sexual orientation in England, Wales, and Northern Ireland, 1995-2002. Adapted from slide from Health Protection Agency ([www.hpa.org.uk](http://www.hpa.org.uk)), Communicable Disease Surveillance Centre. Data from KC60 statutory returns



New diagnoses of selected STIs in men who have sex with men, England and Wales, 1995-2000. Adapted from slide from Health Protection Agency ([www.hpa.org.uk](http://www.hpa.org.uk)), Communicable Disease Surveillance Centre



Cases of infectious syphilis (primary and secondary) seen in genitourinary medicine clinics by sex and male sexual orientation in England, Wales, and Northern Ireland, 1995-2002. Adapted from slide from Health Protection Agency ([www.hpa.org.uk](http://www.hpa.org.uk)), Communicable Disease Surveillance Centre

## Syphilis

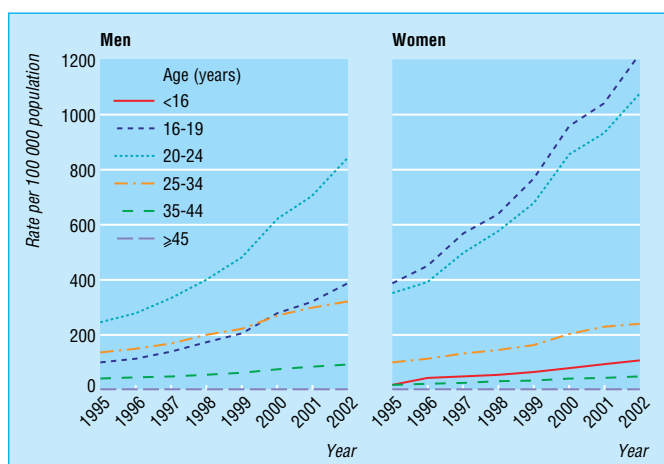
Syphilis is now rare in western Europe and North America, which is mainly due to the control of early acquired infectious syphilis in women and screening of pregnant women for syphilis. In most western European countries the incidence of syphilis has continued to decline to below five per 100 000. As mentioned above, an epidemic of most STIs has occurred in eastern Europe, with a recent epidemic of syphilis in all the newly independent states of the former Soviet Union. This epidemic is the vanguard of an HIV epidemic, and outbreaks of HIV have been reported in intravenous drug users, particularly in Belarus, Russia, and Ukraine. Likewise, syphilis is still a major clinical problem and a cause of genital ulceration in the developing world.

It is of concern that syphilis also is increasing again in the United Kingdom. In the past seven years, the cases of infectious syphilis have increased by 870%, particularly in men heterosexual and homosexual.

## Chlamydia

Chlamydia is still a major public health problem in most of Europe and North America. In the United Kingdom, infection with *Chlamydia trachomatis* is now the most common curable bacterial STI. Since 1996 the number of cases has increased, with cases in women outnumbering cases in men. In 2002, 81 680 people with chlamydial infections attended clinics.

This condition is most commonly seen in young people; the peak age is between 20 and 24 years in men and between 16 and 19 years in women. Screening surveys performed outside normal STI clinic environments also show high levels in antenatal and gynaecology clinics, general practice, and family

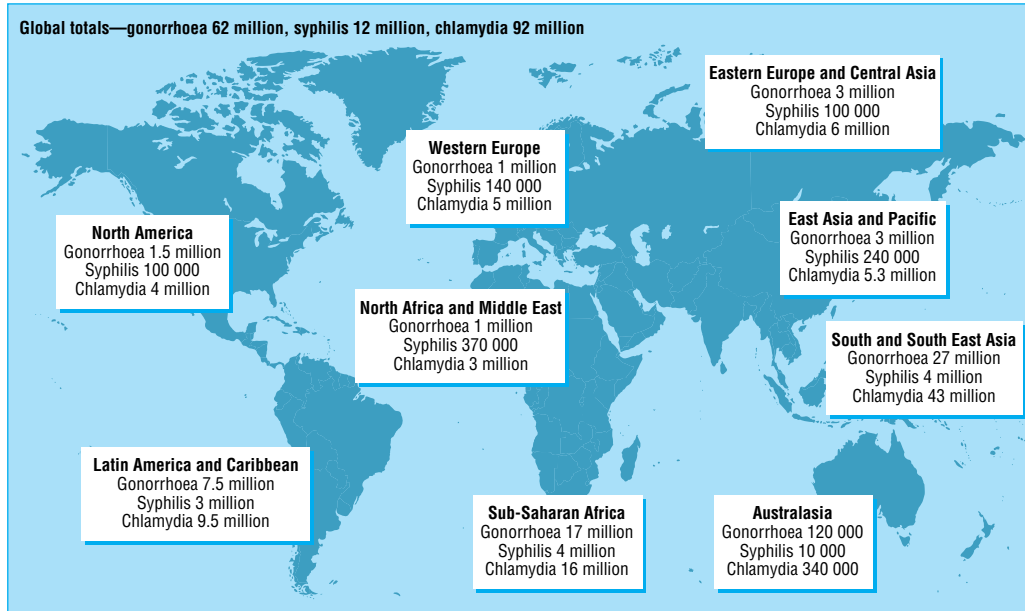


Diagnoses of uncomplicated genital chlamydial infection in genitourinary medicine clinics by sex and age group in the United Kingdom, 1995-2002. Data are unavailable for Scotland for 2000-2. Adapted from slide from Health Protection Agency ([www.hpa.org.uk](http://www.hpa.org.uk)), Communicable Disease Surveillance Centre. Data from KC60 statutory returns and ISD(D)5 data

planning and pregnancy termination clinics, with the prevalence rate ranging from 4.5% to 12%.

**Genital herpes and warts**

Compared with gonorrhoea and chlamydia, the increase in cases of genital herpes and warts has slowed down in British GUM clinics in the past few years.



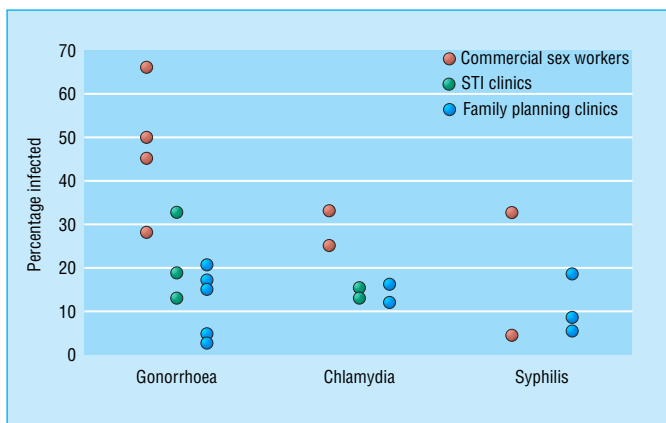
Estimated new cases of the three most common STIs among adults

**STIs in developing countries**

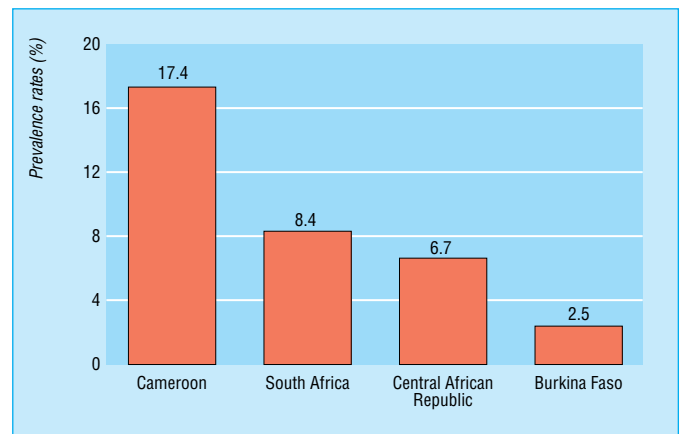
Sexually transmitted infections have a much higher incidence and prevalence in developing countries and are among the top five reasons for consultation in general health services in many African countries. Routine and accurate surveillance data are often lacking, and an understanding of the burden of infection tends to come from WHO estimates and ad hoc surveys, usually in high risk groups.

Particularly high rates of infections are seen in groups such as female prostitutes and their clients and truck drivers. Prostitution continues to be an important factor in the transmission of STIs in developing countries. For example, in an urban Kenyan STI clinic, 60% of men with a diagnosis of gonorrhoea or chancroid reported commercial sex exposure as the probable source of infection. Genital ulcer disease is more

**High rates of syphilis, chlamydia, and gonorrhoea are seen particularly in sub-Saharan Africa and South and South East Asia**



STIs in women in Africa



Syphilis prevalence rates (%) in pregnant women in Africa in 1990s

## ABC of Sexually Transmitted Infections

frequent in developing countries (syphilis, chancroid, lymphogranuloma venereum, and granuloma inguinale), and in sub-Saharan Africa, 20-70% of patients who attend clinics present with ulcers. In commercial sex workers, the prevalence of gonorrhoea can reach nearly 50%, and the prevalence of syphilis ranges from 2% to 30% for acute or previous infection. Infection with herpes simplex virus (type 2) is almost universal among commercial sex workers in various African countries, for example Zimbabwe. Rates of syphilis in women who attend antenatal clinics are high, with rates reaching 17% in Cameroon. Levels of chlamydia can be as high as 30%.

The incidence of STI complications and their sequelae is much higher in developing countries because of the lack of resources and adequate diagnosis and treatment. Particular complications are adverse pregnancy outcomes for mother and baby, neonatal and infant infections, infertility in both sexes, ectopic pregnancy, urethral strictures in males, and blindness in infants caused by gonococcal and chlamydial ophthalmia neonatorum and in adults caused by gonococcal keratoconjunctivitis, as well as genital cancers, particularly cancers of the cervix and penis.

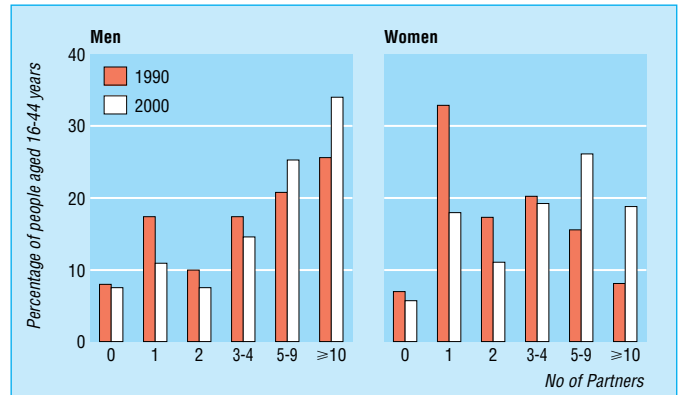
## Why are STIs increasing?

Like many other medicosocial conditions, for example suicide, alcoholism, cancer, and heart disease, the explanation for the increase is multi-factorial. Attitudes towards sex and sexual behaviour have changed. The survey of Sexual Attitudes and Lifestyle carried out in the United Kingdom plotted changes between 1990 and 2000.

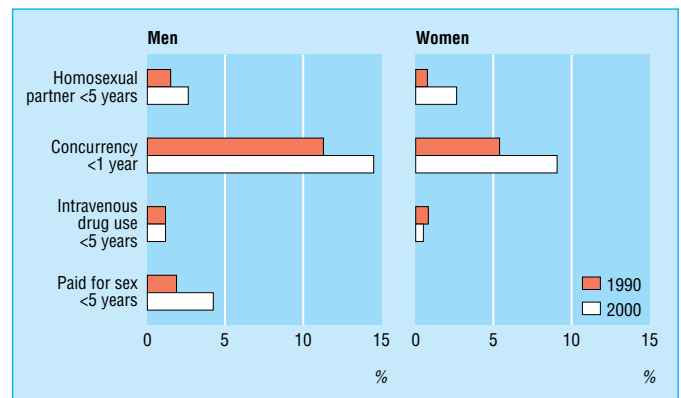
- Age at first intercourse has declined, and half of all teenagers have sex before they are 17 years of age
- The number of lifetime male and female heterosexual partners has increased since 1990, with the highest increases in young people
- The proportion of men and women who have concurrent relationships (having more than one sexual partner at the same time) has increased
- Condom use has increased in the United Kingdom but may be offset by the increase in the number of sexual partners. For example, the proportion of the population who reported two or more partners in the past year and who did not use condoms consistently has increased since 1990 from 13.6% to 15.4% for men and from 7.1% to 10% for women
- The proportion of men in the United Kingdom who have ever had a homosexual partner in the last five years increased between 1990 and 2000. Unsafe sex in homosexual men has increased, particularly in London
- Populations are now more mobile nationally and internationally. Certain groups (tourists, professional travellers, members of the armed forces, and immigrants) are at risk. They are separated from their families and social restraints and are more likely to have sexual contact outside a stable relationship. In addition, poverty, urbanisation, war, and social migration often result in increased levels of prostitution.

## Conclusion

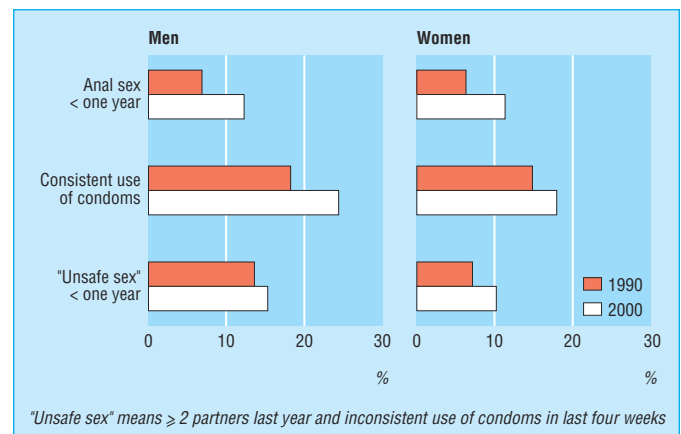
Sexually transmitted infections are a major public health problem throughout the world, in terms of morbidity and mortality and in their facilitatory role in the acquisition and transmission of HIV. Prevention programmes are essential to deal with these issues (see Chapter 2).



Percentage distribution of heterosexual partners in lifetime by sex, 1999 and 2000. Adapted from National Survey of Sexual Attitudes and Lifestyles, 2000



Changes in behaviour over time. Adapted from National Survey of Sexual Attitudes and Lifestyles, 2000



Changes in behaviour over time. Adapted from National Survey of Sexual Attitudes and Lifestyles, 2000

### Further reading

- Adler MW, Cowan FM. Sexually transmitted infections. In: Detek R, McEwen J, eds. *Oxford textbook of public health: the practice of public health*. 4th ed, vol 3. Oxford: Oxford University Press, 2002, pp 1441-52
- Adler M, Foster J, Grosskurth H, Richens J, Slavin H. *Sexual health and care: sexually transmitted infections, guidelines for prevention and treatment*. London: Overseas Development Administration, 1996

# 2 Control and prevention

Frances Cowan

Sexually transmitted infections (STIs) represent one of the major public health problems in the world today, as outlined in Chapter 1. The demographic, sociological, economic, and behavioural changes seen throughout the world in the past 40 years will continue to drive the spread of STIs.

## Pattern of spread

Several factors are known to be important in maintaining the spread of STIs in communities. A simple arithmetic formula has been developed that makes it possible to anticipate the pattern of spread of STIs in communities under certain circumstances. If the average number of infections that result from one infection is greater than one, then the rate of that STI will increase in the community. Conversely, if the average number of infections is less than one, then the rate of spread of the STI will fall. Reductions in any of these variables at a community level will decrease the average number of new infections that result from one infection in that community.

## Principles of control

The approach to controlling STIs and the emphasis placed on different components will depend on the local pattern and distribution of STIs in the community and whether one is working in a setting that is resource rich or resource poor. However, the same general principles will apply.

Prevention can be aimed at uninfected people in the community to prevent them from acquiring infection (primary prevention) or at infected people to prevent the onward transmission of the infection to their sexual partners (secondary prevention). Although effective primary prevention can theoretically reduce the prevalence of viral and bacterial STIs, secondary prevention is much more effective at reducing the prevalence of bacterial STIs, which all are curable with antibiotics. In fact, the population prevalence of a bacterial STI can be reduced entirely through effective secondary prevention activities without any reduction in risky sexual behaviour occurring.

Countries that combine primary and secondary prevention approaches, at the individual and population levels, have managed substantially to reduce the burden of infection in their population. Effective implementation of prevention programmes requires strong political leadership and genuine commitment, without which the most well designed and appropriate programmes are likely to founder. Countries such as Thailand, Brazil, Uganda, and Senegal have seen a dramatic impact on their rates of STIs and HIV, which has been facilitated greatly by political support at the highest level.

Interventions that reduce the rate of STI can be aimed at the entire community or targeted at specific groups who are at high risk of, or are particularly vulnerable to, infection. One to one prevention interventions can take place in clinic settings, as outlined in Chapter 3.

## Primary prevention

Primary prevention interventions aim to keep people uninfected. These approaches are obviously not mutually

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### Determinants of STI spread

$$R_0 = \beta cd$$

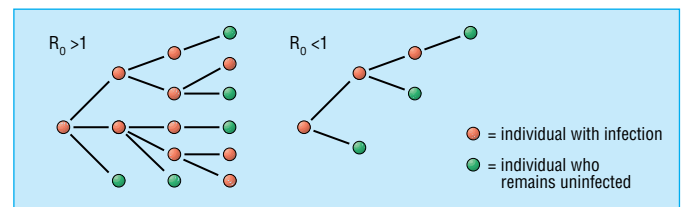
$R_0$  = average number of new infections that result from one infection

$\beta$  = transmissibility

$c$  = average rate of acquiring partners

$d$  = duration of infection

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Pattern of spread

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### Principles of effective STI control

- Reduce infectiousness of STIs
    - Condoms
  - Reduce duration of infection
    - Encourage diagnosis and treatment of symptomatic infection (encourage health seeking behaviour) and asymptomatic infection (screening, partner notification, and mass or targeted treatment)
  - Reduce risky behaviour
    - Reduce rate of partner change
    - Delay onset of sexual intercourse
    - Improve selection of partners
- 

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### Primary prevention

- *Behavioural interventions* are aimed at enhancing knowledge, skills, and attitudes to help people protect themselves against infection (for example, health promotion to decrease partner change and increase condom use)
  - *Structural interventions* are aimed at broader societal and economic issues that drive the spread of STIs
  - *Biomedical interventions* include condoms, vaccines, vaginal microbicides, or male circumcision to prevent the acquisition of infection
-



## ABC of Sexually Transmitted Infections

exclusive. Individual behaviour change probably will be best sustained in a community that is broadly supportive. In addition, the broader cultural mores of the community will influence greatly the feasibility of delivering education in that community and will also affect how people respond to it.

### Education and information

The aim of sexual health promotion is broader than minimising the risks associated with sexual intercourse and other sexual practices. It also aims to facilitate development of healthy sexual behaviour patterns and relationships. Although supplying appropriate and timely factual information is very important and the first step in this process, evidence shows that providing information alone is not enough to bring about a change in behaviour. Widely available information about STIs (or contraception) has not been proved to encourage immoral or promiscuous behaviour.

Health education needs to inform people of the advantages of discriminate and safer sex and the means to prevent or reduce the risk of infection. Although the best way to avoid STIs is to avoid sexual intercourse, this is not a realistic or acceptable message. People need health messages that are tailored to their lifestyles and needs, which allow them to make informed choices about their behaviour. Factors other than lack of knowledge contribute to an individual's ability to practice safer sexual behaviour, however, including perception of health risk, low self esteem, poor self efficacy, peer pressure, and power and sex inequalities. Drug and alcohol use also have an influence. Increasingly, health promotion interventions aim to address some or all of these factors.

That health promotion campaigns address the issues directly related to the infections themselves is also important, including what the various infections are; how to recognise the symptoms; the short and long term consequences of infection; and where to access appropriate advice, diagnosis, and treatment. As most of those infected with an STI have either asymptomatic or unrecognised infection, however, people also need to be aware that they cannot rely on symptoms alone to distinguish infected people from uninfected people and that they themselves can be infected even if asymptomatic.

### Structural or societal interventions

Clearly it may be unrealistic to expect individual behaviour change when the broader societal and cultural context is not supportive of this change.

Structural factors that may hinder behaviour change include physical, social, cultural, organisational, economic, and legal or policy aspects of the environment. For example, interventions that promote condom use and partner reduction strategies for impoverished heterosexual women in developing countries may be impractical, because women lack the power to negotiate condom use, particularly with their regular partners or husbands, and because they may be economically dependent on sex work to provide income for basic necessities, such as food or their children's school fees. In this scenario, interventions need to include men and, more broadly, tackle women's rights regarding inheritance, owning property, and earning income legitimately.

### Biomedical interventions

Male condoms, if used properly and consistently, can reduce the risk of transmission of many STIs. They are more effective for some STIs than for others, however, and their use does not guarantee that infection will not occur. Female condoms are also advocated to reduce STI and HIV transmission and are attractive because they are under the control of the woman,

### Ways for an individual to reduce their risk of contracting an STI

- Abstain
- Have a mutually monogamous relationship with someone who is uninfected
- Select partners whose past and current behaviour puts them at low risk of infection. Consider both being screened for infection before unprotected sex
- Reduce the numbers of sexual partners
- Avoid sex with people who have symptoms of a STI or oral "cold sores"
- Use condoms consistently on every occasion with all partners
- In open relationships couples agree to have only non-penetrative or protected sex outside their main relationship



The Department of Health's website ([www.playingsafely.co.uk](http://www.playingsafely.co.uk)) uses interactive quizzes to show the difficulty in distinguishing infected from uninfected people

**Interventions that are most effective are those that draw on social and psychological theories of behaviour change derived from research that seeks to understand the origins and control of sexual behaviour**

### Structural interventions

These can take place at various levels, including

- Community level (for example, legislating to change the age of consent for homosexual men or inheritance laws)
- Organisational level (for example, providing reproductive health clinics in schools or the workplace)
- Individual level (for example, microfinance initiatives that seek to train women to become less economically dependent)

although evidence of their effectiveness is less than for the male condom.

Hepatitis B vaccine is the only vaccine that effectively prevents acquisition of an STI, although vaccines for other STIs are currently in development or being evaluated. In addition, several other biomedical approaches for reducing the risk of STIs are currently being explored, including presumptive periodic treatment for people who are at high risk of STIs, male circumcision, and vaginal microbicides. However, all these interventions are in the early stages of evaluation.

## Secondary prevention

Secondary prevention interventions aim to reduce the risk of individuals infected with an STI transmitting this infection to their sexual partners. These approaches entail increasing screening and appropriate treatment of symptomatic and asymptomatic people; encouraging health seeking behaviour; and tracing, screening, and treating sexual partners of infected people (contact tracing). Other more experimental approaches have included presumptive treatment of people at high risk of infection.

### Screening and treatment

Early diagnosis and treatment are cheap, whereas the late sequelae of untreated disease are expensive. For example, if gonorrhoea and chlamydial infection (a major cause of pelvic inflammatory disease (PID)) are well controlled, then PID and all its serious long term sequelae can be prevented.

In many parts of the world specialised STI clinics have been established to provide screening and treatment for people with symptoms of, or who feel they are at risk of, an STI. These clinics provide prompt laboratory or microbiological based diagnosis (or both) and treatment, minimise the incidence of complications and disability, trace and treat sexual contacts, and provide education. These are sometimes known as vertical services.

Clearly the extent of screening will vary according to the laboratory facilities available. In most western countries, clinics screen for syphilis, gonorrhoea, chlamydia, *Trichomonas vaginalis*, bacterial vaginosis, and *Candida* as a matter of course and offer HIV antibody testing. Those presenting with symptoms will have additional screening tests (see Chapters 3-7). Screening at an STI clinic, however, does not guarantee that a person is free of all infections. It is not routine to screen asymptomatic individuals for herpes simplex virus or human papillomavirus. Those people found to be infected should be managed according to local treatment guidelines. Increasingly, single dose treatments are available for STIs, and the use of these will maximise compliance and minimise the development of drug resistance.

In countries without access to a laboratory, most people who present to clinic will be symptomatic, and screening may be limited to clinical examination with or without microscopy. The sensitivity and specificity of clinical examination for distinguishing STI causes of genital symptoms from non-STI causes, particularly in women, has improved somewhat by using a system for scoring risk. For example, having had a new partner recently greatly increases a person's risk of contracting an STI. The services are non-specialised and provided as part of other general medical services, for example in primary health centres, maternal and child health centres, and family planning clinics, and by private practitioners, pharmacists, traditional healers, and street



The Department of Health's website ([www.playingsafely.co.uk](http://www.playingsafely.co.uk)) promotes the use of condoms for sexual health

### Secondary prevention

- Enhancing health seeking behaviour
- Improving access to for STIs diagnosis and treatment
- Ensuring appropriate case management
- Early detection and treatment of symptomatic and asymptomatic infection
- Partner notification (contact tracing)

**To be most effective, clinics should be open access and provide confidential, non-judgmental care and appropriate health care for which there is no charge. Health education can be used to enhance health seeking behaviour and to encourage people without symptoms to attend for screening if they are at high risk of infection**

### Specialist services for STIs in the United Kingdom

- Genitourinary medicine—269 clinics and 273 consultants
- Features of service
  - Open access and free
  - Confidential
  - Screening and treatment for STIs
  - Screening and treatment for HIV
  - Contraception and psychosexual problems
  - Miscellaneous care (for example, for urinary tract infections and genital dermatological conditions)
  - Partner notification
  - Health promotion, counselling, and advice
  - Outreach and special services
  - Training and research

# ABC of Sexually Transmitted Infections

vendors. Vertical and integrated services for managing individuals with STIs have both advantages and disadvantages.

In resource poor settings where clinics have limited access to diagnostic facilities, the World Health Organization recommends that the syndromic approach is used for patient management. This uses algorithms based on the common presenting signs and symptoms, for example genital ulceration and urethral or vaginal discharge. Rather than healthcare worker trying to decide on the aetiology of the symptoms on the basis of examination alone, the relevant algorithm shows treatment for all the common STI causes of that syndrome in that setting. Syndromic management algorithms differ in different parts of the world, which reflects the local disease profile and antimicrobial resistance patterns (examples are given in Chapters 5 and 7). In some countries where much of the treatment for STIs is delivered through pharmacists and street vendors, preprepared drug treatment packages have been developed and marketed. These packs include the appropriate drug for the relevant syndrome, a contact slip advising that the sexual partner should be treated, and will often include condoms as well.

In addition to managing people who present with symptoms, the syndromic approach has been supplemented in some settings by presumptively treating people who are at high risk of bacterial STIs with appropriate antibiotics. For example, in South Africa, a programme that provides monthly antibiotic treatment to sex workers seems to have reduced the rates of bacterial STIs among sex workers and their clients. This approach is attractive because it allows treatment of symptomatic and asymptomatic people, although it needs to be evaluated more formally to see if it results in the development of antimicrobial resistance or any other adverse effects. An extension of this is the concept of mass treatment of whole populations who have or might be at risk of STIs.

## Contact tracing

Tracing sexual contacts is an important part of any control programme. Sexual contacts have an increased likelihood of infection with an STI and are often (although not always) unaware that they are infected. It is essential, therefore, to get in touch with contacts as soon as possible and advise them to attend a clinic. Although contact tracing is primarily conducted for its public health benefit, it also is of direct benefit to the people concerned. For someone in an ongoing relationship, treatment of their partner is essential if they are not to become reinfected. If the contact remains unaware of their infection risk, they may go on to develop sequelae of infection or to infect other people unwittingly.

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## Further reading

- Mathews C, Coetzee N, Zwarenstein M, Lombard C, Gutmacher S. Strategies for partner notification for sexually transmitted diseases. *Cochrane Database Syst Rev* 2004;(1):CD002843
- Sumartojo E, Doll L, Holtgrave D, Gayle H, Merson M. Enriching the mix: incorporating structural factors into HIV prevention. *AIDS* 2000;14:S1-2
- Evidence of effectiveness of HIV prevention interventions. *J AIDS* 2002;30:S1-134

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## Vertical services for STIs

### Advantages

- Specialists
- Accurate laboratory diagnosis with appropriate treatment
- Reference laboratory
- Training
- Monitoring, surveillance, and research
- Asymptomatic infection may be detected

### Disadvantages

- Expensive
- Delays in diagnosis
- Limited availability
- Limited coverage of population
- Stigmatisation
- Poor sustainability

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## Integrated services for STIs

### Advantages

- Problem orientated
- Immediate presumptive diagnosis and treatment of possible aetiologies
- Non-specialist
- Inexpensive
- Standardisation of management and monitoring of drug use and antibiotic resistance

### Disadvantages

- Low sensitivity and specificity for cervical gonococcal or chlamydial infection in women
- Asymptomatic infection not detected but treatment possible by active partner notification and epidemiological treatment of partners
- Not always acceptable to medical staff

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## Contact tracing

- *Patient (index) referral*, whereby the patient informs their sexual partners themselves
- *Provider referral*, whereby the index patient asks the healthcare worker to inform partners on their behalf
- *Contract (conditional) referral*, whereby the index patient undertakes to notify partners themselves in a given timeframe. If the partners are not notified in this period, the contact tracer or health adviser will attempt to notify them with the patient's consent. This uses a combination of the patient and provider referral techniques

# 3 The clinical process

Patrick French

People with sexually transmitted infections (STIs) are often asymptomatic or have symptoms that they do not recognise as being related to an STI. They also may not have access to care or be unaware of how to access care. They can be identified in many ways, however, in a wide range of differing services and settings. The most appropriate site for STI care will reflect local epidemiology, the resources available for care, and the pre-existing structure of health services. This will mean that, according to local circumstances, STI care could be provided by primary or secondary care, pharmacies, or outreach services (see Chapter 2). In the United Kingdom, STIs often are managed by specialists in genitourinary medicine in dedicated clinics.

Despite the need for clinical services to reflect diversity, it is also important to ensure that some key principles regarding the care of people with STIs are adopted. They should receive effective treatment and care as promptly as possible. This approach reduces the risk of the patient developing complications and reduces the chances of onward transmission.

Facilitation of the access of people with STIs or at risk of STIs to services that provide assessment and care is an essential step in establishing good control of STIs. Linking services to any health promotion activity in the community that is designed to raise awareness of STIs and establishing care pathways with other non-specialist clinical services are all part of this access strategy.

Another vital component is service advertising. The media used for advertising will depend on the target populations of the local STI programme and the resources available.

Services for people who seek care for STIs should encourage destigmatisation of these conditions and also acknowledge that such stigma exists. Establishing an environment that is confidential, private, and free of judgment encourages openness and allows a full and accurate risk assessment to be undertaken. This lays the groundwork for future care and health promotion.

Care of individuals with STIs often requires the participation of a multidisciplinary team of practitioners including nurses, doctors, administration staff, laboratory workers, and counsellors. Staff who are responsible for helping to identify and trace sexual contacts are an essential part of the team. In the United Kingdom, this work often is undertaken by sexual health advisers. The effectiveness of the team is enhanced greatly by shared clinical guidelines and operational

## Summary of the clinical process

- Presentation to STI service
- Sexual history and risk assessment
- Clinical and genital examination
- Investigations
- Treatment
- Condoms
- Health promotion
- Partner management
- Follow up

## Ways STIs can be identified

- Screening
- Case finding (“opportunistic” screening)
- Presentation to non-STI clinical services
- Presentation (including self referral) to STI services

## Principles of STI care

- Access to care must be easy, rapid, and preferably free
- Systematic risk assessment of all patients is needed
- Investigations should support but not delay care
- Rapid and “bedside” tests are important
- Therapy that is easy to adhere to is preferable (single dose if possible)
- Condom and sexual health promotion
- Partner management



An example of service advertising—Playing Safely website created by the Department of Health, United Kingdom ([www.playingsafely.co.uk](http://www.playingsafely.co.uk))



An example of service advertising—STI care in the developing world

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policies, which include a description of the roles and responsibilities of each staff group.

## Core components of STI assessment

The core components of an STI assessment are history taking (especially sexual history), examination (particularly genital examination), and investigations.

### Sexual history taking

The communication skills required to take a good sexual history are an extension of the skills already possessed by many healthcare workers. It is important to establish rapport and trust between the doctor and patient and to acknowledge that many people find it difficult to discuss their sexual lives openly.

The scope and detail of the sexual history will vary according to the site of care, available resources (particularly consultation time), and the particular patient group being seen. However, to allow for basic risk assessment and further management several crucial components must be discussed. The specific issues that relate to sexual history taking in men and women are detailed in Chapters 5 and 7, respectively.

The sexual history will guide the clinical examination and will allow for a more rational approach to selecting investigations. The sexual history will also form the basis for partner management and sexual health promotion. The period of time over which a sexual history should look back will depend on a number of factors, including duration of symptoms (if any symptoms are present), the date of previous STI assessments, and incubation periods of any STIs diagnosed or suspected. In practice, most clinicians would elicit a risk history for at least the previous three months or until the last partner change, whichever is the longer. Ideally, the sexual history should form part of a wider risk history that should include a general medical history, including current drug use and misuse (including injecting drug use) and allergies. In women cervical cytology, gynaecology, and contraception histories should be taken. For proformas see Appendix on pages 85–6.

### Clinical examination

The clinical examination is an important part of the assessment for an STI and will be guided by the sexual history. Often during the examination, clinical specimens are obtained and some STIs are diagnosed. Sexually transmissible conditions, such as scabies, pediculosis pubis, molluscum contagiosum, and genital warts, are almost always diagnosed clinically; diagnostic procedures are reserved for atypical presentations.

An appropriate environment for an examination is important. It is essential to explain and discuss the purpose and nature of the examination to the patient and to acknowledge that many patients find it distressing and intrusive. Good visualisation of the genital area is vital for a proper examination. However, the autonomy and dignity of the patient must be recognised and protected as much as possible.

### Investigations

The role of the laboratory is discussed in detail in Chapter 17, and sampling during the clinical examination is discussed in Chapter 4.

Diagnostic tests often are taken during the clinical examination but increasingly “non-invasive” tests (including vaginal and vulval tests), in which urine or saliva specimens taken by the patient, are used for diagnosis. Because non-invasive tests are easy to take and samples can be obtained from patients at venues with minimal clinical facilities, they are

**Good management of STIs is not complex but does include a number of important components that need to be addressed during clinical care. For this reason many units have developed proformas to ensure that a systematic and comprehensive approach to management is followed. Such forms also facilitate the routine auditing and improvement of clinical practice**

### Sexual history taking

- Symptoms (including duration)
- Last sexual intercourse
- Sex of partner
- Relationship with partner (casual, long term, traceable, etc)
- Use of barrier contraception
- Sites of exposure (oral, vaginal, or anal)
- Last previous partner or partner change (with site of exposure and barrier contraception history as above)
- Partners' symptoms
- Previous STIs or testing for STIs including HIV

Name:	Date:
Sex:	Number:
Age:	Scen by:
Status:	
Main symptom:	Sexual History:
Previous STI:	Examination findings:
Condom knowledge: Condom use:	
Treatment received so far:	
Drug allergy:	Treatment:
Diagnosis:	
Counselling: Compliance Contacts Condoms STI/HIV prevention	
Follow up:	Signature:

Developing world proforma: a case record can be designed on one page to record essential information about STI patients

### Examination setting

- Clear explanation to patient
- Comfortable for patient and clinician
- Private
- Good illumination
- Chaperoning for patient

**The diagnostic investigations undertaken will depend on the findings during risk assessment and clinical examination, as well as the resources available to the doctor**

particularly well suited to screening and case finding programmes.

In some settings, the most effective form of STI care and control is syndromic management (see Chapters 5, 7, 8, and 11), so that no investigations are taken to establish an aetiological diagnosis. This approach will usually include the components described earlier and health promotion and partner management, but treatment is administered according to local knowledge of the cause or aetiology of the presenting syndrome (such as treating men presenting with urethral discharge for gonorrhoea and chlamydia).

In other environments, rapid and bedside investigations aid diagnosis during the initial clinic visit. These are particularly useful in the rapid diagnosis of urethral gonorrhoea in men and determining the aetiology of vaginal discharge. The range of tests currently undertaken in STI clinics in the United Kingdom is discussed in Chapters 4-7.

## Treatment of STIs

Treatments for STIs need to be effective and administered as promptly as possible. A relatively small number of drugs are needed to provide effective therapy for most of the infections, and this allows many services to develop small onsite dispensaries.

National and international guidelines for STI treatment have been developed to improve and standardise care. They are evidence based and updated on a regular basis. With the exceptions of gonorrhoea and chancroid, little clinically important resistance to the recommended antimicrobials is seen. An effective single dose treatment is now available for most bacterial and protozoal STIs, including gonorrhoea, chlamydia, syphilis, chancroid, and trichomoniasis. This allows onsite observed therapy and removes concerns about treatment adherence.

Treatment for viral STIs is more complex and will often require long term follow up and care. The role of treatment in reducing the infectiousness of viral STIs is being elucidated at present, but it is probable that sexual health promotion and condom promotion have equally important roles.

The dosing schedule, rationale, and possible toxicities must be discussed with the patient, as well as potential interactions with other therapies, for example antibiotics and oral contraceptives.

## Condom and sexual health promotion

A consultation with patients who have STIs or are at risk of developing an STI is a valuable opportunity to provide sexual health promotion, prevention, education, and condom promotion on a one to one basis.

The areas covered in a sexual health promotion discussion will be similar in all consultations but can be tailored to the needs of the individual patient. Hepatitis A and B are currently the only STIs that can be prevented by vaccination (herpes simplex type II infection and HPV-16 vaccines are being developed).

Many STI services and prevention programmes offer hepatitis B vaccination to all STI patients or to some who are perceived as being at particularly high risk of acquiring hepatitis B (see Chapter 15).

**People with STIs or attending STI services are much more likely than the general population to have HIV infection. Offering and recommending HIV testing should be a routine part of all STI consultations**

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### Treatment guidelines\*

- Clinical effectiveness produced by the British Association for Sexual Health and HIV (UK) 2002 ([www.bashh.org](http://www.bashh.org))
- International Union against STIs (European) 2001 ([www.iusti.org](http://www.iusti.org))
- Centers for Disease Control (American) 2002 ([www.cdc.gov/cdc/std/treatment/SumCont.htm](http://www.cdc.gov/cdc/std/treatment/SumCont.htm))
- World Health Organization 2002 ([www.who.int/docstore/hiv/STIManagementguidelines/](http://www.who.int/docstore/hiv/STIManagementguidelines/))

\*All treatment recommendations cited in the text are taken from one or more of the guidelines above

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### Treatment of STIs

#### Features of effective therapy

- Prompt administration
- Observed therapy or single dose treatment
- Well tolerated or easy adherence
- Guidelines followed (local gonorrhoea or chancroid sensitivities)

#### Treatment discussion

- Nature or rationale of therapy
  - Written information
  - Treatment adherence
  - Sexual abstinence during treatment
  - Partner notification
  - Follow up (if needed)
- 

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### Sexual health promotion

- Behaviour change
  - Safer sex and risk reduction
  - Condom promotion
  - Hepatitis B vaccination
  - Future STI care
-

## Partner management

All patients with STIs will have had at least one partner who currently has or who has previously had an infection. Partner notification is an essential part of care (see Chapter 2). Encouraging the sexual partners of patients with an STI to attend for assessment, treatment, and care reduces the risk of reinfection of the index patient, allows identification of STIs in individuals who are asymptomatic or who have unrecognised symptoms, and provides an opportunity to discuss sexual health promotion with someone at high risk of an STI.

Partner notification entails a sensitive discussion that relies on establishing trust between the patient and healthcare worker. The rationale and importance of partner notification should be explained clearly to the patient. Most patients will take on the responsibility of informing their sexual contacts (patient referral), but some patients may request or need the clinic to undertake partner notification on their behalf (provider referral).

Contact slips and written information for patients and their sexual contacts may facilitate this process. Mechanisms for monitoring the outcome of partner management should be established.

## Follow up

Many patients with infections will need follow up care. This may be related to directly reviewing the outcome of previous treatment and the management of viral STIs. However, it may also include testing for STIs with long incubation periods (such as HIV and syphilis) and further health promotion activity.

It is essential that follow up appointments check for

- Symptom resolution
- Treatment adherence
- Further sexual exposure
- Partner notification resolution
- Test of cure or treatment response
- Further STI screening
- Health promotion.

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London, WC1E 6AU

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	Tues	9.00a.m. - 11.00a.m.
	Wed	3.45p.m. - 7.00p.m.
	Thurs	9.00a.m. - 6.00p.m.
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If you would like to speak to a health professional, in confidence, about this slip please ring 020 7530 5111.

This is a free and confidential service.

**PLEASE BRING THIS SLIP WITH YOU WHEN YOU ATTEND AND GIVE TO THE DOCTOR**

**FOR CLINIC USE ONLY**

INDEX REF NO. _____	CONTACT REF NO. _____
DATE _____	DATE _____
KC60 CODE _____	KC60 CODE _____

**PLEASE RETURN TO HEALTH ADVISERS DEPARTMENT, MORTIMER MARKET CENTRE**

Contact slip

The developing world proforma is adapted from *Providing Health Services in Sexual Health Interventions*. West Bengal: Project Management Unit of the West Bengal Sexual Health Project, 1998.

# 4 Examination techniques and clinical sampling

Patrick French

The general principles and appropriate environment for the examination were covered in Chapter 3. In practice, the examination of patients in a clinic is often confined to the genitals, but if a sexually transmitted infection (STI) that has extragenital manifestations is suspected (such as scabies, syphilis, or HIV), then a general examination will also be necessary, even if the patient has no symptoms outside the genitalia. This examination will concentrate on the skin, mouth, and lymph nodes but a more thorough examination is essential if the late complications of HIV or syphilis are suspected.

## Examination of the male patient

Examination of the male genitalia may be done standing (useful for hernia and varicocele) or lying. It should include

- inspection of areas covered with hair for pediculosis pubis
- examination of genital skin for ulceration, inflammation, warts, and molluscum contagiosum
- palpation of inguinal lymph nodes for enlargement and tenderness
- retraction of the prepuce and a search for subpreputial skin lesions (such as chancre or warts) and balanitis
- urethral meatus for discharge and meatitis (the patient or doctor may try to squeeze out the discharge)
- palpation of the testes and epididymes to diagnose epididymo-orchitis and screen for testicular cancer.

The anus should be inspected externally for warts that occur in both homosexual and heterosexual males. Men who report anal symptoms, receptive anal intercourse, or receptive oroanal sexual contact should undergo proctoscopy to inspect the anal and rectal mucosa for inflammation, pus, or ulcers. Digital examination may assist in diagnosing prostatic disorders, such as cancer and prostatic inflammation.

As previously mentioned, clinical sampling often will be taken during examination, and the routine tests taken are described below. Other tests will be dictated by clinical presentation and local epidemiology. All patients should be offered and recommended serological tests for syphilis and HIV (after pre-test discussion).

## Sampling of the male patient

### Urethra

A plastic loop is inserted to a depth of 2 cm and smeared on to a glass slide for Gram staining and enumeration of polymorphs to diagnose urethritis. It can then be streaked on to gonococcal culture medium. A second specimen is taken for chlamydia testing.

### Urine

All tests listed above can also be done on a spun urine deposit. Some services use leucocyte esterase testing to indicate a possible diagnosis of urethritis.

### Throat (if indicated)

A Dacron tipped swab is taken from the tonsillar crypts and posterior pharynx and plated on to gonococcal culture medium. Gram stained smears from this site are not helpful.

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## General examination

### Skin

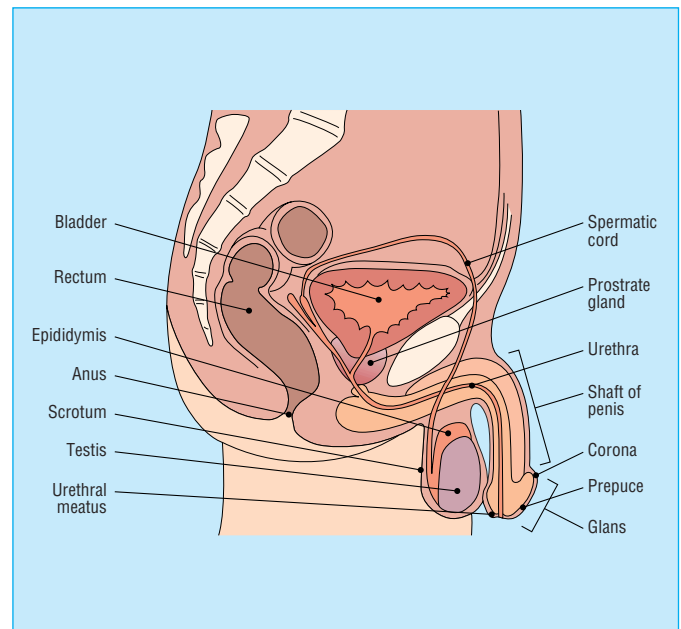
- Scabies—rash (especially on wrists, between the fingers, and on the buttocks and areolae)
- Secondary syphilis and HIV (seroconversion illness)—generalised rash and lesions on palms and soles

### Lymph nodes

- Secondary syphilis, HIV, and primary herpes simplex—generalised lymphadenopathy

### Mouth

- Secondary syphilis—ulceration and mucous patches
  - HIV—oral hairy leukoplakia, oral candidiasis, Kaposi's sarcoma, and angular cheilosis
  - Herpes simplex—ulceration
  - Warts
- 



Male genitalia including scrotal contents (adapted from *Sexually transmitted infections: history taking and examination* CD, The Wellcome Trust, 2003)



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### Rectum (if indicated)

The rectal mucosa is sampled through a proctoscope with a plastic loop that is smeared on to a glass slide for Gram staining and streaked on to gonococcal culture medium.

### Prostate (if indicated)

Sampling prostatic fluid requires firm massage of the prostate gland with a gloved finger inserted in the rectum to express prostatic secretions through to the urethral meatus. Material obtained can then be examined in stained smears and cultured.

## Examination of the female patient

Examination of the female patient begins with an inspection of the external genitalia, followed by vaginal and cervical examination after passing a vaginal speculum (usually a Cusco speculum). Finally, a bimanual pelvic examination is done.

### External genitalia

- Examine genital skin for inflammation, ulcers, warts, molluscum contagiosum, and pediculosis pubis
- Examine vestibule and introitus for any discharge or Bartholin's cyst or abscess
- Palpate inguinal lymph nodes.

### Cervix and vagina

- Inspect discharge
- Examine vaginal walls for inflammation
- Examine cervix for ectropion, cervicitis, and mucopurulent discharge.

### Pelvis

- Examine uterus and cervix for pain on palpation or movement
- Examine for adnexal tenderness and masses.

## Sampling of the female patient

### Vagina

Vaginal discharge samples are taken from the posterior fornix with a small plastic loop. The discharge is tested with narrow range pH paper and potassium hydroxide to help elucidate the cause of the vaginal discharge.

A further vaginal sample is examined in wet preparation for *Trichomonas vaginalis* and clue cells and with gram stain for *Candida albicans*. The vaginal sample is sent for *T vaginalis* and *C albicans* culture.

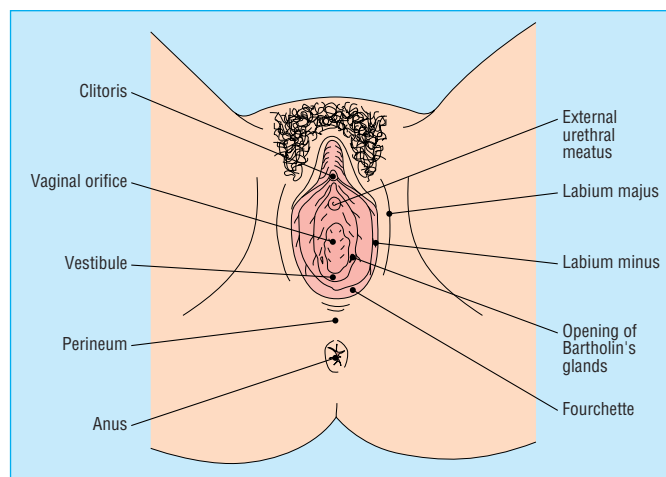
### Cervix

After mucus and secretions have been wiped off the cervix with a cotton wool ball, the endocervix is sampled. A loop is used to take a sample for Gram staining and *Neisseria gonorrhoeae* culture. A further swab is taken for the identification of *Chlamydia trachomatis*.

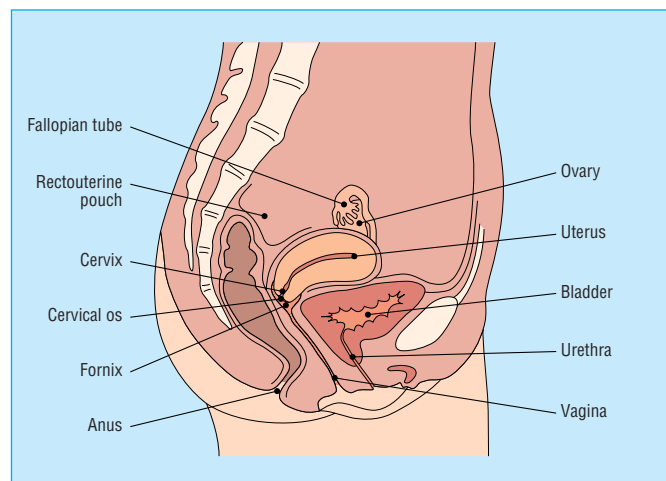
### Urethra

A small plastic loop is used to collect a sample from the proximal urethra that is smeared on to a glass slide for Gram staining and streaked on to a slide for *N gonorrhoeae* culture.

A full description of laboratory diagnostic tests used in the field of STIs is given in Chapter 17.



Female external genitalia (adapted from *Sexually transmitted infections: history taking and examination* CD, The Wellcome Trust, 2003)



Female internal genitalia (adapted from *Sexually transmitted infections: history taking and examination* CD, The Wellcome Trust, 2003)

**Proctoscopy and tests for *N gonorrhoeae* should be done for all women who report anal sex**

# 5 Main presentations of sexually transmitted infections in male patients

John Richens

Some sexually transmitted infections (STIs), such as gonorrhoea and chlamydial infection, have very different presentations in the two sexes because of differences in genital anatomy. This chapter focuses on infections of the male urethra, epididymis, testis, and prostate. Anal and oral symptoms are also covered because these are encountered more often among men, especially men who have sex with men. Chapter 6 deals with a variety of other genital symptoms in men that usually are not related to STIs but often come to the attention of healthcare professionals who work in sexual health services.

## Urethral discharge and dysuria

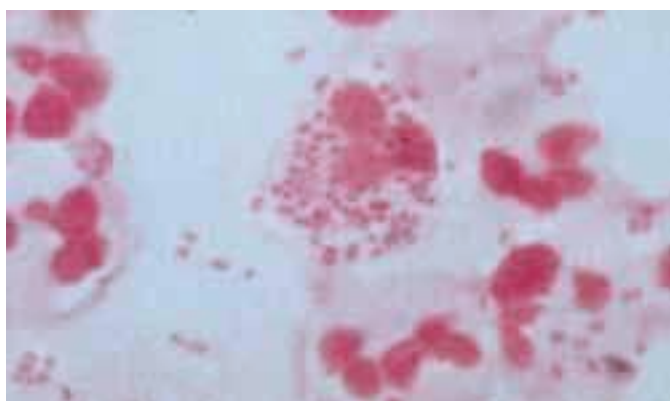
Spontaneous discharge of fluid from the urethral meatus, usually most noticeable after holding the urine overnight and often accompanied by burning discomfort during urination (dysuria), strongly indicates a sexually acquired urethral infection.

Symptomatic gonorrhoea usually develops in a few days of exposure. *Chlamydia* infections take slightly longer. Mild infections may cause urethral discomfort and dysuria without discharge and may be confused with cystitis.

### Management of urethritis in male patients

- 1 Take history, including sexual history
- 2 Examine, looking especially for evidence of discharge
- 3 Take samples from urethra
- 4 Treat for gonorrhoea and chlamydia if urethral Gram stain is positive for Gram negative intracellular diplococci
- 5 Give treatment for *Chlamydia* if the urethral smear shows five or more polymorphs per high power field and the Gram stain does not suggest gonorrhoea
- 6 Explain diagnosis, treatment, and methods of prevention
- 7 Advise to avoid sex until treatment and follow up are completed
- 8 Advise partner treatment
- 9 Review patient after treatment for symptoms, adherence, treatment of partners, and test of cure if gonorrhoea has been diagnosed

Where laboratory investigation is not feasible, steps 3, 5, and the test of cure can be omitted



Gram negative intracellular diplococci

### Causes of urethritis in men

#### Common diagnoses among men with urethritis

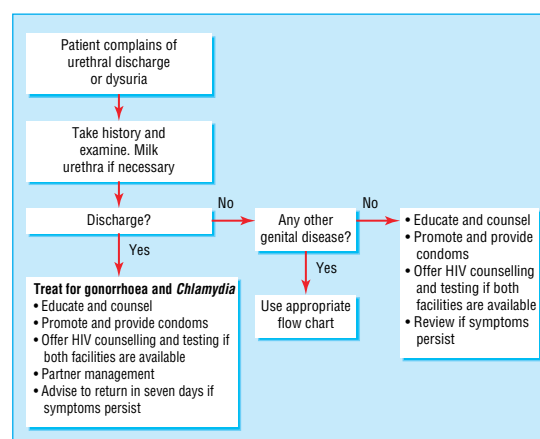
- Gonorrhoea
- Chlamydial infection
- Non-specific urethritis

#### Less common diagnoses among men with urethritis

- *Ureaplasma urealyticum* infection
- *Mycoplasma genitalium* infection
- Trichomoniasis
- Herpes simplex virus infection
- *Escherichia coli* infection
- Bacteroides infection
- Cystitis
- Pyelonephritis
- Trauma
- Foreign body
- Reactive arthritis, Reiter's syndrome, and allied conditions



Gonococcal urethral discharge



Urethral discharge flow chart (World Health Organization)

## Overview of chlamydial and gonorrhoea infection

### Chlamydia

#### Cause

- *Chlamydia trachomatis*, types D-K (see also lymphogranuloma venereum, p 45). *C trachomatis* is an obligate intracellular bacterium

#### Initial sites of infection

- Epithelial cells of urethra, cervix, rectum, pharynx, and conjunctiva depending on mode of exposure

#### Incubation period

- Less than four weeks for men; unknown in women
- Asymptomatic infections are common in both sexes and can persist for many months

#### Main symptoms in men

- Urethral discharge and dysuria

#### Less common symptoms in men

- Proctitis, conjunctivitis, epididymo-orchitis, and reactive arthritis

#### Main symptoms in women

- Dysuria, vaginal discharge, and intermenstrual bleeding

#### Less common symptoms in women

- Pelvic inflammatory disease (with sequelae of infertility and ectopic pregnancy), perihepatitis (Fitz-Hugh-Curtis syndrome), and conjunctivitis

#### Symptoms affecting neonates

- Conjunctivitis and pneumonia

#### Main methods of diagnosis

- Enzyme immunoassay and DNA amplification (ligase chain reaction (LCR) and polymerase chain reaction) (see Chapter 17)

#### Recommended treatments for uncomplicated Chlamydia

- Doxycycline: 100 mg twice daily for seven days (C, E, U, W)
- Azithromycin: 1 g single dose (C, E, U, W)
- Erythromycin base: 500 mg twice daily for 14 days (E (2), U(2))
- Erythromycin base: 500 mg four times daily for seven days (C (2), E(2), U(2), W)
- Erythromycin ethylsuccinate: 800 mg four times daily for seven days (C(2))
- Tetracycline: 500 mg four times daily for seven days (U(2), W)
- Ofloxacin: 200-300 mg twice daily or 400 mg once daily for seven days (C(2), E(2), U(2), W)
- Levofloxacin: 500 mg daily for seven days (C)
- Amoxicillin: 500 mg three times daily for seven days has been validated in pregnant patients (C, E, U, W)

#### Follow up testing

- Not recommended routinely and should not be done before three weeks if PCR or LCR is used, because these tests can detect non-viable organisms

(C = Centers for Disease Control, USA; E = European STI guidelines; U = UK National Guidelines; W = World Health Organization; (2) = second line recommendation).

In clinics with laboratory facilities, the usual approach is to test for gonorrhoea and chlamydial infection. The first step is microscopy of a urethral smear. Optimal results for this are obtained from patients who have held their urine for four hours or more.

Urethritis is confirmed if the urethral smear shows five or more polymorphs per high power field. If the smear shows Gram negative intracellular diplococci, the patient is treated for gonorrhoea and *Chlamydia* to cover the possibility of a mixed infection. Meanwhile, confirmatory tests for gonorrhoea and *Chlamydia* are carried out (see Chapter 17).

Patients without evidence of gonorrhoea receive doxycycline (100 mg twice daily for one week), erythromycin (500 mg twice daily for two weeks), or azithromycin (1 g single

## Gonorrhoea

#### Cause

- *Neisseria gonorrhoeae*, a Gram negative coccus
- Initial sites of infection: columnar epithelium of urethra, endocervix, rectum, pharynx, or conjunctiva depending on mode of exposure

#### Incubation period

- Two to five days in 80% of men who develop urethral symptoms
- Asymptomatic infections common in both sexes, especially infections of pharynx, cervix, and rectum

#### Main symptoms in men

- Urethral discharge, dysuria, and tender inguinal lymph nodes

#### Less common genital symptoms in men

- Epididymo-orchitis, abscesses of paraurethral glands, and urethral stricture

#### Main symptoms in women

- Vaginal discharge, dysuria, abnormal bleeding
- Examination may show mucopurulent discharge from the cervical os, urethra, Skene's glands, or Bartholin's glands

#### Less common genital symptoms in women

- Lower abdominal pain and vulvovaginitis (pre-pubertal girls)

#### Extragenital symptoms and complications that affect both sexes

- Pharyngitis, rectal pain and discharge, and conjunctivitis
- Disseminated infection involving skin, joints, and heart valves, secondary infertility after damage to Fallopian tubes, or epididymis

#### Main methods of diagnosis

- Detection of Gram negative intracellular diplococci in smears and culture for *N gonorrhoeae*

#### Treatments recommended for uncomplicated gonorrhoea in the following guidelines

- Ciprofloxacin: 500 mg single dose by mouth (C, E, U, W)
- Ofloxacin: 400 mg single dose by mouth (C, E, U, W)
- Levofloxacin: 250 mg single dose by mouth (C)
- Ceftriaxone: 125 mg single dose given intramuscularly (C, E, U(2), W)
- Cefotaxime: 500 mg single dose given intramuscularly (C(2), U(2))
- Cefixime: 400 mg single dose given by mouth (C, E, W)
- Spectinomycin: 2 g single dose given intramuscularly (C(2), E, U(2), W)
- Ampicillin: 2 g or 3 g plus probenecid 1 g as a single oral dose (U, E(2)) (in areas with <5% resistance to penicillin)

#### Resistance

- Resistance to penicillin and tetracyclines is widespread
- Resistance to quinolones is increasing and resistance to azithromycin and spectinomycin has been reported
- Choice of treatment should take into account local susceptibility data

#### Follow up

- A test of cure culture is recommended when available



*N gonorrhoeae* culture

dose), which are active against chlamydial infection and most other pathogens associated with non-gonococcal urethritis. Doxycycline can cause photosensitivity. Absorption is impaired by antacids, iron, calcium, and magnesium salts. Gastrointestinal upset is common with erythromycin and azithromycin.

This approach will relieve symptoms in most patients, but some will report persistent symptoms or show a persistently abnormal smear without symptoms. The options are then to investigate for treatment failure or reinfection or for infection by less common pathogens (for example, *Trichomonas vaginalis*) and to repeat, continue, or change the antibiotic therapy or await spontaneous resolution of symptoms.

When access to laboratory testing is not available, the simplest approach to managing urethritis is to administer blind treatment for gonorrhoea and *Chlamydia*.

## Scrotal swelling and pain

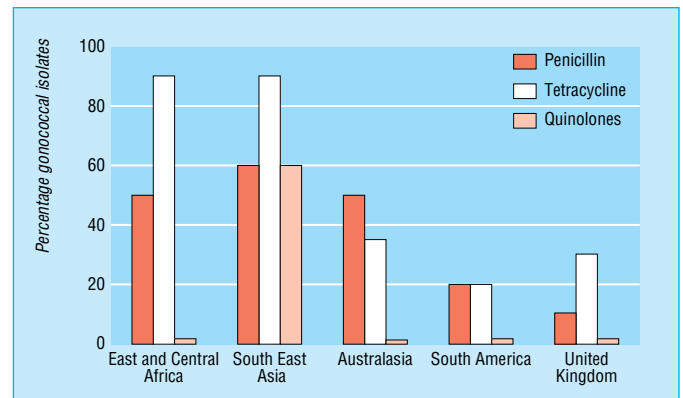
Mild testicular discomfort in the absence of abnormal physical signs is encountered commonly in young male attenders in STI clinics. Many such patients can be reassured if testicular examination and a screen for STIs are carried out and found to be normal. In some cases, anxiety about infection, sexual function, or cancer is present. More marked scrotal pain has a variety of causes.

Acute inflammation of the scrotal contents (usually unilateral) in young men is usually caused by gonorrhoea or *Chlamydia*. In older men, *Escherichia coli*, klebsiella, pseudomonas, and proteus are found more often. The first consideration in diagnosis is to exclude acute torsion, which requires emergency surgery. Torsion predominates in the teenage years, usually has an acute onset, and is often accompanied by vomiting. An immediate surgical opinion should be sought for any possible case. Doppler scanning is useful for demonstrating impaired blood flow. The distinguishing features of a mumps orchitis are usually onset several days after parotid swelling, severe testicular pain, and marked systemic symptoms, although the parotitis may be absent. Useful tests for cases of suspected epididymo-orchitis are a urethral smear, mid stream urine culture, and investigations for gonorrhoea and chlamydia. Presumptive treatment for gonorrhoea and chlamydia is appropriate in younger males when investigation is not feasible. Severe cases require treatment in hospital with parenteral antibiotics. Analgesia, scrotal support, and elevation may reduce discomfort and promote recovery.

Painless swellings in the scrotum are common. Most of these are small, round, epididymal cysts or spermatoceles that require no investigation or treatment. Lesions in the testis can be due to tuberculosis, syphilis, or malignancy and require urgent ultrasound examination. Varicoceles feel like a bag of worms in the scrotum and can be associated with infertility. Therefore, referral to a urologist is advised if pain, testicular atrophy, infertility, or the threat of infertility are concerns.

## Pelvic pain in the male

The prostate can be affected by a variety of infectious and poorly defined non-infectious conditions that present as acute or chronic pelvic pain with a range of accompanying urinary and systemic symptoms. Gonorrhoea, chlamydial infections, and trichomoniasis can affect the prostate, but most acute infections are caused by other bacteria such as *E coli*, proteus, *Streptococcus faecalis*, *Klebsiella*, and *Pseudomonas*. STIs and non-sexually transmitted bacterial infections of the prostate



Antimicrobial resistance of *N gonorrhoeae* in selected countries in the 1990s

### Causes of scrotal swelling and pain in adults and adolescents

- Infections of testis and epididymis: gonorrhoea, *Chlamydia*, tuberculosis, mumps virus, and Gram negative bacteria
- Torsion of testis (mainly adolescents) or appendix testis (mainly three to seven year olds)
- Pain after vasectomy
- Fournier's gangrene
- Vasculitis: Henoch-Schönlein purpura, Kawasaki disease, and Buerger's disease
- Amiodarone therapy
- Tumour
- Hernia
- Trauma



Acute epididymo-orchitis due to STI

### Measures occasionally found helpful in men with chronic pelvic pain syndrome

- Simple analgesia
- Non-steroidal anti-inflammatory drugs
- Two to four weeks of ciprofloxacin or doxycycline
- Alpha blocking drugs (alfuzosin, terazosin, tamsulosin)
- Finasteride
- Quercetin
- Low dose amitriptyline
- Repetitive prostatic massage (contraindicated in bacterial prostatitis)
- Regular ejaculation

## ABC of Sexually Transmitted Infections

account for only a few painful prostatic syndromes. Most patients with prostatic pain fall into a category recently designated “chronic pelvic pain syndrome” (CPPS) by the newly adopted National Institutes of Health (NIH) classification of prostatitis syndromes.

In patients who present with pelvic pain, the prostate should be examined for enlargement and tenderness. Patients with prostatitis should undergo a normal screen for STIs. The value of subjecting patients to the unpleasant procedure of prostatic massage to examine prostatic secretions for bacteria and inflammatory cells is now questioned by many experts. Transrectal ultrasonography and urodynamic studies are helpful in some patients. Confirmed infections respond well to antibiotics, the first choice often being a 28 day course of a quinolone or tetracycline, which have better prostatic penetration than other antibiotics.

Treating the more common CPPS is difficult. None of the treatments are well validated, and response rates are often poor. A recently published NIH symptoms index for chronic prostatitis is a useful way to record and monitor symptoms.

## Anal symptoms

### Anorectal STIs

Sexually transmitted infections can be transmitted by penile-anal contact, oroanal contact, or fingering, resulting in asymptomatic infection, ulceration (for example, herpes and syphilis), warts, or proctitis, the main manifestations of which are pain, tenesmus, bleeding, and discharge. Ulceration is investigated in the same way as genital ulceration (see Chapter 11). Discharges require investigation by proctoscopy, during which samples can be taken from the rectum to test for *Gonorrhoea* and *Chlamydia*. The management of a sexually acquired rectal discharge parallels that of urethritis. Anorectal infections are a potent cofactor for HIV transmission.

Anal intercourse can lead to the transmission of a wide variety of other organisms normally transmitted by the faeco-oral route. These include hepatitis A, *Shigella*, *Salmonella*, and *Giardia*. Anal intraepithelial neoplasia and invasive carcinoma may follow infection with certain subtypes of human papillomavirus.

### Non-infectious anal conditions

Patients who practise receptive anal sex often present to STI services with anal fissure, haemorrhoids, perianal haematomas, and pruritus ani. It is important to provide training and guidelines for the management and referral of these common conditions in clinics that see clients who practise anal sex.

### Oral and perioral symptoms

Oral STIs usually are asymptomatic. *Gonorrhoea* and *Chlamydia* infect the pharyngeal mucosa readily but rarely cause acute inflammation. Primary syphilis may present on the tongue or lips, and secondary syphilis can produce an oral mucositis. HIV has an important array of oral manifestations that include oral candidiasis (both erythematous and pseudomembranous), angular cheilitis, gingivitis, oral hairy leucoplakia, and Kaposi's sarcoma. Warts may develop in and around the mouth as a result of orogenital sexual activity.

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### Differential diagnosis of prostatic pain (NIH classification of prostatitis syndromes)

- I Acute bacterial prostatitis
- II Chronic bacterial prostatitis
- III CPPS
- IIIA CPPS, inflammatory (leucocytes in prostatic secretion, semen, or urine after prostatic massage)
- IIIB CPPS, non-inflammatory (as above without leucocytes)
- IV Asymptomatic inflammatory prostatitis

#### Other causes of pain in region of prostate

- Pudendal neuralgia (sometimes due to tumour)
  - Bladder outlet obstruction
  - Bladder tumours
  - Urinary stone disease
  - Inguinal ligament enthesopathy
  - Ejaculatory duct obstruction
  - Seminal vesicle calculi
  - Bowel disorders
- 



Rectal gonorrhoea



Perioral warts. With permission of the Wellcome Trust

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## 6 Other conditions of the male genital tract commonly seen in sexually transmitted infection clinics

John Richens

### Conditions affecting the glans and prepuce

The glans and prepuce are susceptible to many local and generalised skin conditions. Mild irritation often responds to simple advice to avoid soap, wash with a weak salt solution, and use emollients. A number of other conditions respond to topical steroid treatment. Persistent conditions may require biopsy because a number of chronic skin conditions of the glans can undergo malignant transformation. The insertion of rings through the urethral meatus (the “Prince Albert”) has become popular in recent years. Such rings rarely give rise to local infections; however, infections are more likely to be associated with anal rings.

### Infectious conditions

*Candida* balanoposthitis can produce soreness, pruritus, erythema, and fissuring. Dry, dull, red, glazed plaques and papules, sometimes eroded, may be seen. The condition is often linked to diabetes. Treatment with an imidazole cream (see Chapter 20) is recommended, together with advice to avoid soap and to bathe with water. Treatment of infected partners has not been shown to benefit men or women with symptomatic *Candida* infection.

### Bacterial infections

Purulent infections of the glans are most often seen in uncircumcised males with phimosis. Important organisms involved include anaerobes, streptococci, staphylococci, and *Gardnerella*. Treatment according to microbiological reports is recommended. When a foul smelling discharge is present, anaerobic infection is likely and treatment with metronidazole 400 mg twice daily for one week is recommended.

### Dermatoses of the glans penis

Any persistent lesion that fails to respond to simple measures should undergo biopsy. Three histologically similar forms of penile intraepithelial neoplasia (carcinoma in situ) of the male genitalia have been described. They are the erythroplasia of Queyrat, which produces velvety plaques on the glans, Bowen’s disease, characterised by erythematous plaques on the shaft or more proximally, and Bowenoid papulosis, which produces multiple lesions after infection with human papilloma virus type 16. Lichen sclerosus (in men sometimes called balanitis xerotica obliterans) produces striking white patches on the glans that may undergo malignant transformation. Treatment is with strong topical steroids and, occasionally, circumcision and meatotomy for cases complicated by phimosis and meatal stricture. Other steroid responsive conditions of the glans are plasma cell (Zoon’s) balanitis, which produces



Ring through the urethral meatus



*Candida* balanitis



Erythroplasia of Queyrat

## ABC of Sexually Transmitted Infections

painless red-orange coloured plaques with “cayenne pepper” spots, lichen planus, psoriasis, and seborrhoeic dermatitis, clues to which are found in the presence of characteristic lesions at other body sites, and circinate balanitis, which is characterised by “geographical” areas of erythema on the glans with white margins. It is linked to other features of Reiter’s syndrome. Fixed drug eruptions occasionally are confined to the penis, the best known cause being the tetracyclines.



Lichen sclerosus



Zoon's balanitis



Psoriasis



Lichen planus



Circinate balanitis



Fixed drug eruptions

## Phimosis, paraphimosis, and lymphocoele

A painful inability to retract the prepuce can result from any chronic inflammatory condition of the prepuce. The condition can be relieved by application of topical steroids or surgical means. Paraphimosis results from prolonged retraction of the prepuce, which leads to constriction of the distal shaft and oedema of the glans. In the early stages, the prepuce can be pushed back by applying firm pressure. This is made easier by first reducing the swelling with ice packs, compression bandaging, or local injections of hyaluronidase. Late cases may require multiple needle puncture and expression of fluid under local anaesthetic (Dundee technique) or surgical intervention.

The term lymphocoele is used to describe a lesion of unknown aetiology that feels like a transverse thrombosed lymphatic vessel close to the corona. This harmless condition develops quite quickly (often after vigorous sex) and resolves spontaneously, usually in a few days.



Lymphocoele

## Common lesions of scrotal skin

Angiokeratomas are harmless small papules with a deep-red or purplish colour, which increase in number with age. Multiple epidermal (sebaceous) cysts are sometimes observed on the scrotum. These conditions are usually left untreated.

## Tinea cruris and erythrasma

Tinea cruris is a superficial fungal infection that affects the skin of the groin; it is seen mostly in men. Patients complain of soreness and itching. Examination shows a well demarcated discoloration of the affected skin. Fungal hyphae can be seen in skin scrapings. Treatment with topical or oral imidazole drugs clears the infection.

Erythrasma is a bacterial condition caused by *Corynebacterium minutissimum*. It occurs in the same area as tinea cruris but tends to have a browner colour and a less well demarcated edge. Porphyrins produced by the bacteria give the lesion a coral pink colour when viewed by Wood's light. It can be treated with erythromycin.



Angiokeratoma

## Semen abnormalities

The observation of blood in the ejaculate causes considerable anxiety. The great majority of cases settle quickly and no underlying disease is detected. A screen for sexually transmitted infections (STIs), urinalysis, examination of prostate, and a blood pressure check are advised. Further investigation is only indicated if symptoms persist. It very occasionally can be associated with hypertension or rare conditions involving the male genital tract in older men. Abnormal lumpiness of semen has been described in patients infected with *Schistosoma haematobium*. A history of exposure to potentially contaminated water in tropical areas should be followed by investigation for schistosomiasis. Patients with prostatitis sometimes complain of changes in semen colour or consistency or ejaculatory pain. It is common to encounter individuals from South Asia who are convinced that they are losing semen unnaturally, giving rise to feelings of lethargy and tiredness. This condition is known as "dhat" in India and is sometimes dignified with the pseudoscientific name "prostatorrhoea." It is closely bound up with cultural concepts of semen and vitality and has no identifiable organic basis.



Tinea cruris



### Peyronie's disease

Fibrosis in the tunica albuginea of the penile shaft can give rise to deformity, which is accentuated during erection. Patients complain of deformity and sometimes pain and difficulty with intercourse. The diagnosis is made by palpating thick fibrous plaques in the penile shaft. Surgery may be required for some patients.

### Disorders of male sexual function

A study of new heterosexual male attenders at a London genitourinary medicine clinic in London in 1997 found that 24% of patients reported sexual dysfunction. Disorders of sexual function are often psychological; however, neurological, endocrinological, and other disorders contribute to a considerable proportion of cases of erectile dysfunction.

Sexually transmitted infections rarely interfere directly with sexual function, although concerns about STIs or HIV often are expressed by patients with dysfunction. Loss of libido and erectile dysfunction are reported commonly by men infected with HIV and may be exacerbated by antiviral treatment.

Once an individual has experienced sexual dysfunction, performance anxiety readily develops, which exacerbates the problem. Reducing performance anxiety is a key aim of psychological therapies.

### Erectile dysfunction

Patients complain of failure to achieve or maintain an erection. Psychological factors can be identified by careful history taking. If the patient does not experience spontaneous erections on waking and cannot masturbate to orgasm, an organic disease is more likely.

Patients should be evaluated carefully for the possibility of organic disease, including measurement of blood pressure, genital examination, and, in some cases, peripheral pulse and neurological examinations. Screening for diabetes and dipstick urinalysis is recommended for all patients. In selected cases, measuring free plasma testosterone (patients with small testes or who report low libido), blood lipids, haemoglobin electrophoresis, follicle stimulating hormone, luteinising hormone, prolactin, thyroid, renal, and liver function tests, or vascular imaging may be indicated.

Treatment options (for which guidelines have recently been published in the *BMJ*) include psychosexual counselling, intracavernosal or intraurethral alprostadil, or oral sildenafil. Mechanical devices and surgical treatments are used occasionally. Treatment should be supervised by specialist centres that can arrange prompt referral for dangerous (albeit rare) complications of therapy, such as priapism.

### Premature ejaculation

An organic cause is unlikely to be found. Therapy is usually behavioural and involves training the patient to delay ejaculation by using a variety of graduated stop-start exercises first, alone, using masturbatory exercises, and then with a partner.

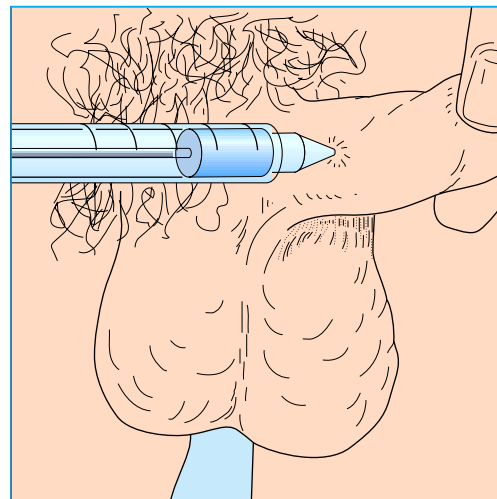
The best known approach with partners is the "sensate focus" technique pioneered by Masters and Johnson, which initially prohibits genital contact and progresses gradually to more intimate contact as more control is achieved. As an alternative, clomipramine and other antidepressants can be taken four to six hours before intercourse with some benefit.



Peyronie's disease caused by the presence of a dorsal plaque in the penis. Reproduced from Tomlinson J (ed) *ABC of sexual health*

### Conditions that can cause disorders of male sexual function

- Hypertension
- Sickle cell disease
- Vascular disease (for example, Leriche syndrome)
- Diabetes
- Neurological disease (for example, multiple sclerosis)
- Endocrine disease (for example, deficiencies of testosterone, gonadotrophins, hypothyroidism, and prolactinoma)
- Alcoholism and substance abuse
- Liver and kidney diseases
- Adverse effects of drugs (for example, antihypertensive and antidepressant medication)
- After prostate and abdominal surgery



Intracavernosal injection of alprostadil. Reproduced from Tomlinson J (ed) *ABC of sexual health*

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# 7 Vaginal discharge—causes, diagnosis, and treatment

Helen Mitchell

Vaginal discharge is a common presenting symptom seen by doctors in many services (primary care, gynaecology, family planning, and departments of genitourinary medicine (GUM)). Vaginal discharge may be physiological or pathological. Although abnormal vaginal discharge often prompts women to seek screening for sexually transmitted infections (STIs), vaginal discharge is poorly predictive of the presence of an STI. This chapter focuses on the causes and diagnosis of vaginal discharge and treatment of the most common infective causes.

## Aetiology

### Physiological discharge

Normal vaginal flora (including lactobacilli) colonise the vaginal epithelium and may play a role in defence against infection. They maintain the normal vaginal pH between 3.8 and 4.4. The quality and quantity of vaginal discharge may alter in the same woman in cycles and over time; each woman has her own sense of normality and what is acceptable or excessive for her.

### Pathological vaginal discharge

Vulvovaginal candidiasis is a common infective cause of vaginal discharge that affects about 75% of women at some time during their reproductive life, with 40-50% having two or more episodes. Bacterial vaginosis is one of the most common diagnoses in women attending GUM clinics. As 50% of cases of bacterial vaginosis are asymptomatic, the true prevalence of this condition in the community is uncertain. Bacterial vaginosis is associated with a new sexual partner and frequent change of sexual partners. A reduced rate of bacterial vaginosis is seen among women in monogamous sexual relationships, but it can occur in virginal women. Increased rates of bacterial vaginosis occur in certain groups of women, such as black African women, lesbians, and smokers.

Recurrence of bacterial vaginosis after treatment is common and can be increased by personal hygiene practices, such as vaginal douching, that disrupt the normal vaginal flora. Bacterial vaginosis may also be associated with concurrent STIs, commonly *Trichomonas vaginalis*. Bacterial vaginosis is associated with pelvic infection after induced abortion and in pregnancy with pre-term delivery and low birth weight (see Chapter 9). Trichomoniasis is less common in affluent countries but reaches high levels (often 10-20%) among poor women in developing countries as well as among disadvantaged women in affluent countries. Although vulvovaginal candidiasis and bacterial vaginosis often develop independently of sexual activity, trichomoniasis is mainly sexually transmitted and has been ranked by the World Health Organization as the most prevalent non-viral STI in the world, with an estimated 172 million new cases per annum.

### What may influence physiological discharge?

#### Age

- Pre-pubertal
- Reproductive
- Post-menopausal

#### Hormones

- Hormonal contraception
- Cyclical hormonal changes
- Pregnancy

#### Local factors

- Menstruation
- Post partum
- Malignancy
- Semen
- Personal habits and hygiene

### Pathological vaginal discharge

#### Infective discharge

##### Common causes

- Organisms
  - *Candida albicans*
  - Bacterial vaginosis
  - *Trichomonas vaginalis*
  - *Chlamydia trachomatis*
  - *Neisseria gonorrhoeae*
- Infective conditions
  - Acute pelvic inflammatory disease (see Chapter 8)
  - Post-operative pelvic infection
  - Post-abortion sepsis
  - Puerperal sepsis

##### Less common causes

- Human papillomavirus
- Primary syphilis
- *Mycoplasma genitalium*
- *Ureaplasma urealyticum*
- *Escherichia coli*

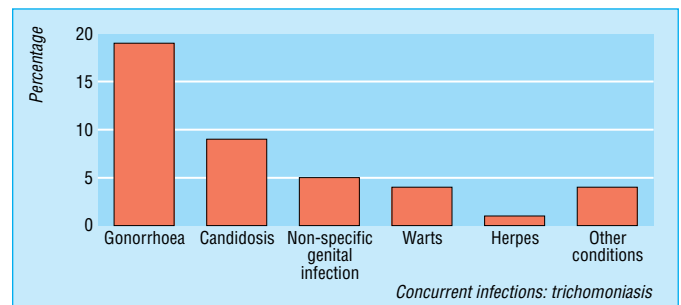
#### Other conditions

##### Common causes

- Retained tampon or condom
- Chemical irritation
- Allergic responses
- Ectropion
- Endocervical polyp
- Intrauterine device in situ
- Atrophic changes

##### Less common causes

- Physical trauma
- Vault granulation tissue
- Vesicovaginal fistula
- Rectovaginal fistula
- Neoplasia



Concurrent STIs found in a survey of women with *T. vaginalis*

## Overview of genital candidiasis and bacterial vaginosis

### Genital candidiasis

#### Cause

- *Candida albicans* in 80-95% of cases; *C. glabrata* in about 5%

#### Associated conditions

- Diabetes mellitus, pregnancy, antibiotic usage, and immunosuppression

#### Transmission

- Mostly non-sexual

#### Site of infection

- Vulva, vagina, glans, prepuce, and rectum

#### Symptoms in women

- Vulvar pruritus, white curdy discharge with “cottage cheese” appearance and sour milk odour, external dysuria, and superficial dyspareunia

#### Symptoms in men

- Soreness, pruritus, redness, and fissuring of glans and prepuce

#### Examination findings in women

- Redness, fissuring, excoriation of vulva, swelling of labia, intertrigo, and lichenification. Thick, white, adherent discharge with vaginal wall erythema

#### Examination findings in men

- Dry, dull, red, glazed plaques and papules on glans and prepuce

#### Main methods of detection

- Fungal hyphae and budding yeasts in smears and culture

#### Recommended intravaginal treatments for women

- Treatment regimes offer 80-95% clinical and mycological cure rates in acute vulvovaginal candidiasis in non-pregnant women
- Vaginal
  - Butoconazole 2% cream 5 g for one to three days (C)
  - Clotrimazole pessary 500 mg single dose (C, E, U, W), 200 mg for three days (C, E, W), or 100 mg for six to seven days (C, U, W)
  - Econazole pessary 150 mg for one to three days (U)
  - Miconazole ovule 1.2 g single dose (E, U)
- Recurrent infection
  - Nystatin vaginal pessary 1-200 000 units for two weeks (C, U) or fluconazole 100 mg per week (see recurrent vaginal *Candida*)
- Recommended oral therapies
  - Fluconazole 150 mg single dose (C, E, U, W)
  - Itraconazole 200 mg twice daily for one day (E, U)
- Topical symptomatic relief suitable for both sexes
  - Clotrimazole 1% cream
  - Miconazole nitrate 2%
  - Clotrimazole 1% with 1% hydrocortisone
- A large number of other preparations are available

## Principles of management

As mentioned, self reported symptoms and the clinical appearance of vaginal discharge are both very variable and do not permit accurate determination of the presence or absence of a specific STI. If a full screen to exclude STIs is not carried out this, may lead to delayed diagnosis and possible long term complications.

An assessment of an individual woman’s STI risk can be made by taking a sexual history. A practitioner working in a primary care setting can then decide whether it is appropriate to refer a woman with identified risk factors in her history directly to a GUM clinic for further management.

The advantage of managing vaginal discharge in a GUM clinic is that full microbiological tests are done to establish an accurate diagnosis. Microscopy is also carried out routinely for symptomatic cases, so an immediate diagnosis will be available for many women.

### Bacterial vaginosis

#### Cause

- Bacterial vaginosis has a polymicrobial aetiology. Organisms involved in the aetiology of bacterial vaginosis include anaerobes *Mobiluncus* sp. and *Prevotella* sp., *Gardnerella vaginalis*, and *Mycoplasma hominis*

#### Main symptoms

- Vaginal discharge with fishy odour that increases after unprotected sexual intercourse and with menstruation

#### Main methods of diagnosis

- Amsel’s diagnostic criteria (three out of four of these criteria need to be present to diagnose bacterial vaginosis)
  - Vaginal pH >4.5
  - Homogeneous grey vaginal discharge
  - 10% potassium hydroxide produces fishy odour “whiff test”
  - Clue cells present on wet mount
- Nugent’s diagnostic criteria (see Chapter 17)
- Note that culture for *Gardnerella* is no longer a recommended approach to diagnosis

#### Recommended treatments

- Treatment regimes have similar cure rates of 70-80% after four weeks. Compliance with therapy may result in a symptomatic cure but not a microbiological cure, so relapse after single dose metronidazole (2g) treatment is common; 60% of women relapse in three months
- Clindamycin is effective but also kills lactobacilli, and topical treatment may predispose patient to vulvovaginal candidiasis. Intravaginal clindamycin can cause condom failure
- Metronidazole 2 g single dose (C (2), E (2), U, W (2))
- Metronidazole 400 mg twice daily for five to seven days (C, E, U, W)
- Metronidazole 0.75% gel daily for five days (C, E, U, W (2))
- Clindamycin 2% cream 5 g daily for seven days (C, E, U, W (2))
- Clindamycin ovules 100 mg daily for three days (C)
- Clindamycin 300 mg orally twice daily for seven days (C, E, W (2))
- Prophylaxis for surgical interventions: rectal metronidazole 1 g or intravenous metronidazole 500 mg

C = Centers for Disease Control, USA; E = European STI guidelines; U = UK National Guidelines; W = World Health Organization, (2) = second line recommendation.

## Questions to ask women who complain of vaginal discharge

### Discharge

- Onset
- Duration
- Amount
- Colour
- Blood staining
- Consistency
- Odour
- Previous episodes

### Associated symptoms

- Itching
- Soreness
- Dysuria
- Intermenstrual or post-coital bleeding
- Lower abdominal pain
- Pelvic pain
- Dyspareunia—superficial and deep

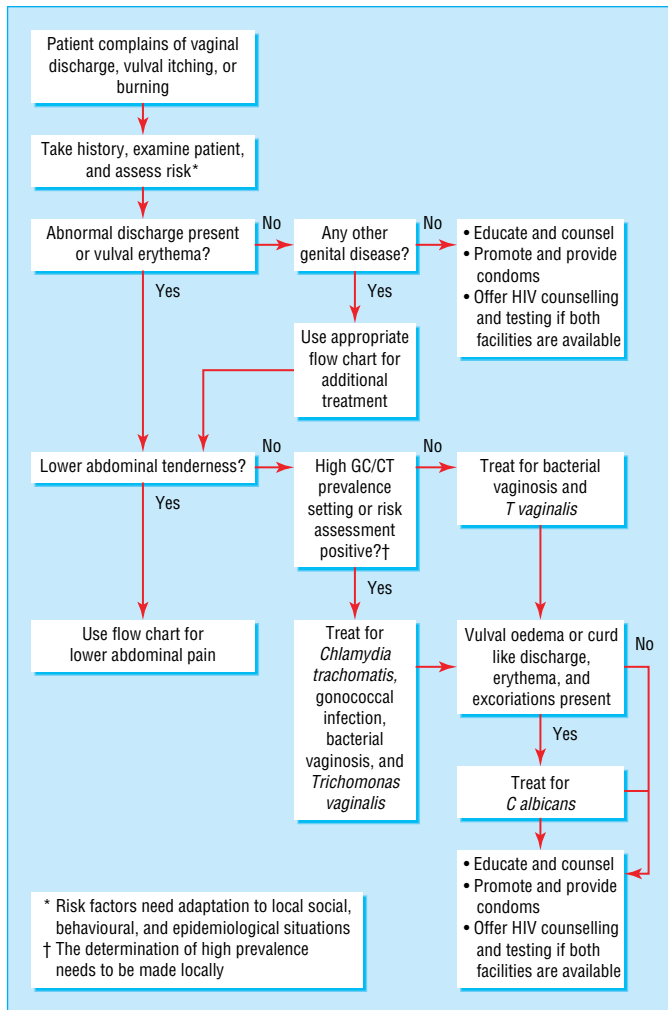
## Risk factors for presence of STIs

- Age under 25 years
- No condom use
- Symptoms developed after recent change of sexual partner or multiple contacts
- Recurrent or persistent symptoms
- Symptoms in partner
- Symptoms imply complications
- Partner’s risk behaviour

The presence of lower abdominal pain, cervical excitation pain, and adnexal tenderness in association with abnormal vaginal discharge implies pelvic inflammatory disease (see Chapter 8).

### Syndromic management

Syndromic management is based on the symptoms and signs that a client presents with and can be undertaken without laboratory support. A flow chart is used to guide the healthcare provider to the most appropriate treatment choice for a given set of symptoms and signs in a woman with a specifically defined risk history. Ideally, these flow charts are based on the local prevalence of STIs, their associated risk factors, and antibiotic sensitivities.



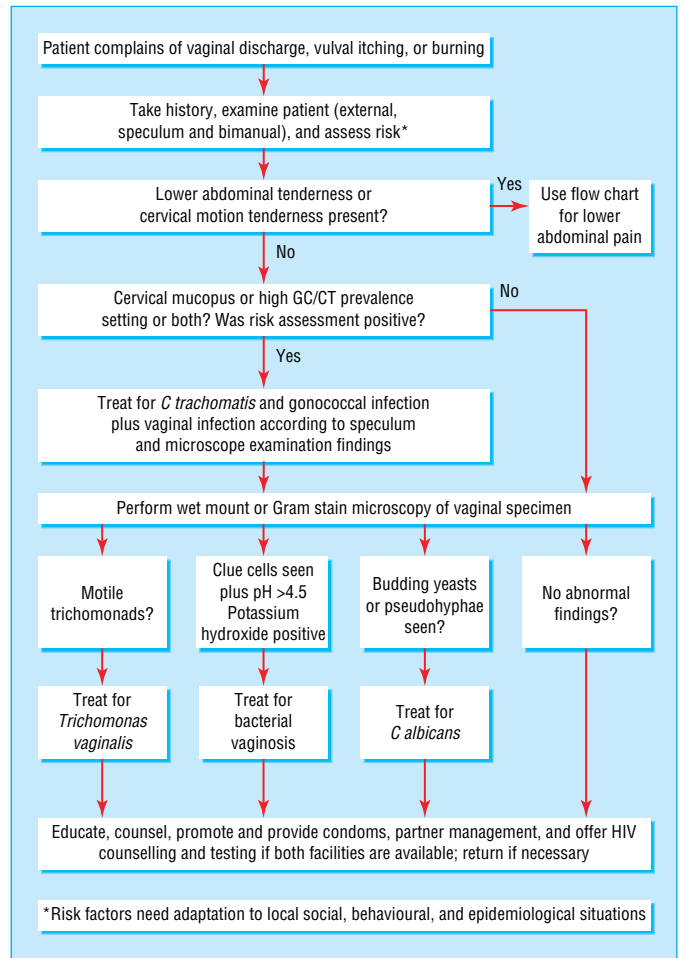
Vaginal discharge flow chart. GC/CT = gonorrhoeal/chlamydial infection

### Investigations

Where laboratory facilities are available a woman with abnormal vaginal discharge should be investigated for gonorrhoea, *Chlamydia*, trichomoniasis, bacterial vaginosis, and candidiasis with samples taken from the vagina and cervix (see Chapters 3 and 4).

### Treatment

Women with vulvitis caused by vulvovaginal candidiasis may respond best to a combination of intravaginal and topical therapy. It should be noted that some of these treatments,



Vaginal discharge flow chart (bimanual, speculum, and microscope). GC/CT = gonorrhoeal/chlamydial infection. Both vaginal discharge flow charts are adapted from the World Health Organization guidelines found at [www.who.int/docstore/hiv/STIManagemntguidelines](http://www.who.int/docstore/hiv/STIManagemntguidelines)



Examples of treatments for vaginal candidiasis

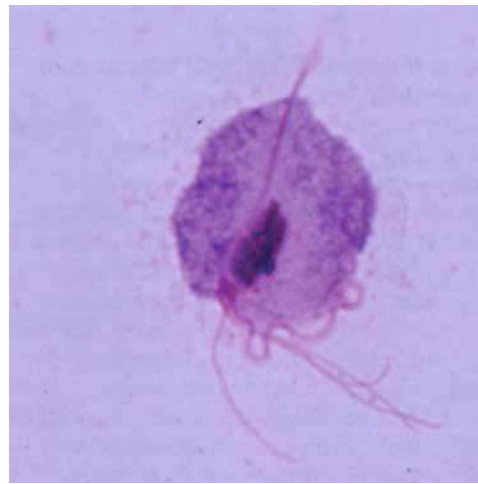
# ABC of Sexually Transmitted Infections

e.g. miconazole and econazole, have an adverse effect on latex condoms, which could cause condom failure. Oral metronidazole, which is used for treating both bacterial vaginosis and *T vaginalis*, is associated with a metallic bad taste in the mouth, gastrointestinal disturbance, and a disulfiram reaction with alcohol. Patients should be advised to avoid alcohol during and for 48 hours after treatment. In the past, questions have been raised about the safety of metronidazole in pregnancy, especially during the first trimester. The current British treatment guidelines advise that no toxicity in pregnant humans has been established. Treatment of symptomatic patients during pregnancy may produce more benefit than harm, and low dose treatment can be used in the first trimester, where clinical indications are present.

## Management

Many women self diagnose and self treat episodes of vaginal infection with over the counter treatments and may subsequently present with a history of “recurrent thrush”, never having had this diagnosis confirmed by microbiological tests.

It is important to confirm the diagnosis and ensure that a full sexual health screen has been done to exclude concurrent infection. Management of vaginal discharge requires an empathic approach with reassurance and psychological support as necessary.



*Trichomonas vaginalis*

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### Overview of trichomoniasis

#### Cause

- *Trichomonas vaginalis*, a flagellated protozoan

#### Incubation period

- Usually seven days (range 3-21 days)

#### Transmission

- Usually sexual. *Trichomonas* may be acquired perinatally. Infection in pre-pubescent girls is unusual, and the possibility of sexual abuse should always be considered

#### Symptoms in women

- Can be asymptomatic. Classically, profuse, frothy, yellow vaginal discharge but also can be scant and watery. Associated symptoms include marked vulvar irritation or soreness (or both), external dysuria, and superficial dyspareunia

#### Symptoms in men

- *T vaginalis* can cause relapsing non-gonococcal urethritis. *T vaginalis* in men can be asymptomatic and has a spontaneous cure rate of about 20-25%, which results in a low rate of isolation in male contacts of about 30-40%

#### Examination findings

- External genital examination may be normal in men and women
- Vulvar and vaginal wall erythema may be present; the “strawberry cervix” appearance caused by inflammatory punctate haemorrhage is uncommon

#### Main methods of diagnosis

- Direct microscopy of discharge and culture

#### Recommended treatments

- Metronidazole 2 g orally stat dose (C, E (2), U, W)
- Tinidazole 2 g orally single dose (W)
- Metronidazole 400 mg orally twice daily for five to seven days (C, E, U, W (2))
- Tinidazole 500 mg orally twice daily for five days (W (2))
- World Health Organization recommends five days’ treatment in preference to single doses for men
- Cure rates 95%
- Compliance can be a problem with the longer regimen because of the nausea and metallic taste in the mouth associated with metronidazole treatment
- In cases of allergy, no effective alternative to imidazole compounds exists
- Patients should be advised to abstain from sexual intercourse during treatment and until their sexual partner has been seen

#### Follow up

- A test of cure should be done at one week with microscopy and culture

#### Management of contacts

- Sexual contacts should be offered a screen for *T vaginalis* and other STIs and given epidemiological treatment with metronidazole 2 g oral stat dose

#### Treatment failure

- Recalcitrant trichomoniasis can result from poor compliance with treatment, reinfection, and poor absorption of treatment, for example because of vomiting
- Longer courses of oral metronidazole or higher dose regimens 2 g a day for three to five days may be effective. Unusually imidazole resistant strains may be responsible.
- No standard effective treatments are available for recalcitrant *T vaginalis* infection.  $\beta$  haemolytic streptococci in the vagina may contribute to metronidazole treatment failure and empirical treatment with amoxicillin or erythromycin before retreatment should be considered in such cases

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C = Centers for Disease Control, USA; E = European STI guidelines; U = UK National Guidelines; W = World Health Organization; (2) = second line recommendation.

## Recurrent vulvovaginal candidiasis

Recurrent vulvovaginal candidiasis is defined as four or more episodes of symptomatic infection annually, which occurs in 5% of healthy women. *Candida glabrata* and other non-albicans species are found in 10-20% of cases. It is important to consider the following

- Medical conditions, such as diabetes mellitus, frequent antibiotic use, and long term steroid therapy
- Vulvar symptoms may be caused by an underlying genital dermatological condition, such as dermatitis or lichen sclerosus
- Immunosuppression, for example HIV infection
- *Candida* species sensitivities if there is an azole resistant isolate. Intravaginal nystatin or boric acid pessaries are alternative treatment options
- An association between atopy, particularly allergic rhinitis, and increased severity of symptoms in recurrent vulvovaginal candidiasis has been described.

## Recurrent bacterial vaginosis

Women may report psychosexual symptoms with lack of libido and anxiety about infection as a consequence of recurrent episodes of bacterial vaginosis and associated malodour.

The bacteria responsible do not persist in the male partner, and concurrent treatment of the male partner does not affect the rate of relapse.

Condom use with male sexual partners may help reduce the risk of recurrence of bacterial vaginosis. Use of hormonal contraception does not increase the incidence of bacterial vaginosis. Women with an intrauterine contraceptive device or system in situ have an increased risk of bacterial vaginosis. Women who use the diaphragm that have *Escherichia coli* urinary tract infections also have an increased incidence of concurrent bacterial vaginosis.

Once again, no robust evidence supports the various alternative treatments available. However, some evidence exists to support the use of intravaginal acetic acid preparations in the management of recurrent bacterial vaginosis.

## Persistent vaginal discharge

It can be difficult to know what to do for women who complain of persistent vaginal discharge with repeated negative STI screens and negative cervical cytology. When minimal discharge is evident on examination, it is worth discussing once again personal hygiene practices and douching, the basis for physiological discharge and enquiring whether there are psychosexual difficulties as a result of the patient's continued symptoms.

If use of spermicides and lubricants is contributing to symptoms, then alternative contraception choices should be discussed. An extensive cervical ectropion can cause heavy mucoid discharge, which, if troublesome to a woman with normal cervical smears, may be helped by intravaginal acetic acid. Some cases may warrant cryocautery to relieve symptoms.

After the menopause, atrophic vaginal changes may predispose women to infective vaginitis. Intravaginal oestrogen replacement, with pessaries or cream, gradually will improve the condition of the vaginal epithelium and reduce the susceptibility to infection.

Underlying gynaecological disease must be considered in all women with unexplained persistent vaginal discharge. Gynaecological neoplasms, such as benign endocervical and endometrial polyps, can present with vaginal discharge, and malignancy needs to be excluded.

Referral to a gynaecologist allows for further investigations that may include transvaginal ultrasonography, endometrial sampling, and hysteroscopy.

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### What can we offer women with recurrent vulvovaginal candidiasis?

- Longer courses of treatment or empirical self treatment with an intravaginal azole at identified cyclical trigger points over a three month period
  - Maintenance treatment regimes
    - Fluconazole 100 mg weekly for six months
    - Clotrimazole 500 mg pessary weekly for six months
  - Non-albicans species may respond to intravaginal nystatin pessaries for 14 days
  - Modifying the allergic component of the problem
    - Hydrocortisone ointment 1% topically
    - Antihistamines may relieve nocturnal irritation and scratching (chlorpheniramine 4 mg orally)
- 



Candidal vulvovaginitis

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### What can we offer women with recurrent bacterial vaginosis?

- Give a clear explanation about bacterial vaginosis
  - Carefully go through their daily personal hygiene practices to identify those that may disrupt the normal balance of vaginal flora
  - Explain that although short course treatments often relieve symptoms, the imbalance in bacteria may persist, and this is why symptoms can recur after treatment
  - A longer course of antibiotics such as metronidazole (400 mg) twice daily for up to seven days can be more effective in preventing or delaying recurrence
  - Explore the impact on the patient's personal and sexual life and offer psychological support and psychosexual counselling when appropriate
  - If a woman with recurrent bacterial vaginosis has an intrauterine device in situ, alternative contraception could be discussed
- 

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# 8 Pelvic inflammatory disease and pelvic pain

Helen Mitchell

Acute pelvic inflammatory disease (PID) is most commonly caused by infection ascending from the vagina or cervix, which causes inflammation of the upper genital tract. This can result in any combination of salpingitis, endometritis, oophoritis, parametritis, pelvic peritonitis, and tubo-ovarian abscess formation.

The organisms commonly responsible for acute PID depend on the local prevalence of sexually transmitted infections (STIs). *Chlamydia trachomatis* is the most common treatable bacterial STI in the United Kingdom and is implicated in more than 50% of cases of acute PID. Ten to 20% of cases are associated with *Neisseria gonorrhoeae*, this rate will be higher in areas with higher local prevalence. Studies have shown that 8-39% of women with *C trachomatis* related genital infection will develop acute PID. In addition, it is estimated that for every overt case of chlamydial pelvic infection there are three covert (asymptomatic) cases.

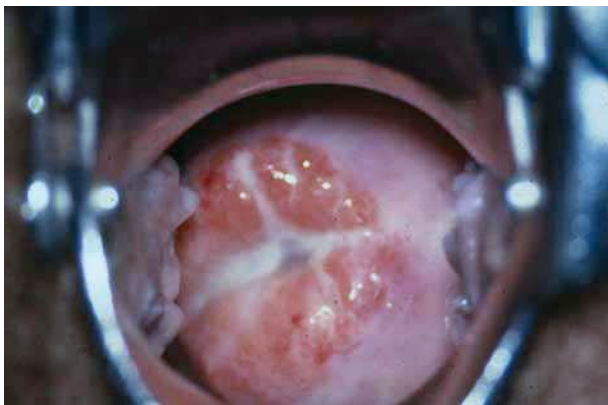
The role of *Mycoplasma genitalium* and *Ureaplasma urealyticum* in acute pelvic infection is still unclear, but they have been implicated in the pathogenesis of acute endometritis and chorioamnionitis associated with pre-term labour.

Other organisms connected with acute pelvic infection include anaerobes, *Bacteroides fragilis*, peptostreptococci, *Escherichia coli*, and Lancefield group B haemolytic streptococci. Bacterial vaginosis is associated with ascending infection and acute PID after induced abortion and post partum.

## Clinical diagnosis of PID

The most common presenting symptoms are lower abdominal pain and abnormal vaginal discharge. Other symptoms associated with PID include intermenstrual and post-coital bleeding, dysuria, deep dyspareunia, and fever. Low backache and rectal discomfort may also be present. Right upper quadrant pain from perihepatitis is a feature of the uncommon Fitz-Hugh-Curtis syndrome in association with *C trachomatis* related PID.

The history for pain should include onset, site, and nature, as well as aggravating and relieving factors. A full menstrual, contraception, and gynaecological history should be taken to make a risk assessment for unplanned pregnancy, including ectopic pregnancy, and ovarian disease. The sexual history will provide a risk assessment for the presence of an STI. It is also important to ask about urinary or bowel symptoms.



Mucopurulent cervical discharge with cervicitis

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### Differential diagnosis of lower abdominal pain

- Ectopic pregnancy
  - Urinary tract infection
  - Ovarian cyst complications—torsion and rupture
  - Endometriosis
  - Ovarian malignancy
  - Bowel disease
  - Irritable bowel syndrome
  - Appendicitis
- 

---

### Risk factors for PID in patient's history

#### Presence of an STI

- New sexual partner in past month
- Frequent change of sexual partner
- No condom use
- Age under 25 years
- Partner with symptoms
- Previous medical history of an STI
- Involuntary infertility

#### Gynaecological interventions that can cause ascending infection

- Intrauterine contraceptive device insertion or change in 20 days
  - Termination of pregnancy—induced abortion
  - Hysterosalpingogram
  - Endometrial sampling
  - Hysteroscopy
  - Dilatation and curettage
  - Evacuation of retained products of conception
- 

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### Clinical diagnosis of PID

#### Presenting symptoms

- Lower abdominal pain
- Abnormal vaginal discharge
- Intermenstrual or post-coital bleeding (or both)
  - Dysuria
  - Backache
  - Fever

#### With additional clinical signs from list below

- Adnexal tenderness
  - Cervical excitation pain
  - Mucopurulent cervical discharge
    - Pyrexia above 38°C
    - Rebound
    - Guarding
    - Adnexal mass
-

A history of abdominal surgery for infertility, ovarian disease, appendectomy, and bowel disease can provide useful diagnostic pointers. If the onset of lower abdominal pain has occurred after a recent gynaecological intervention, then the intervention may have introduced an infection or transmitted an infection from the cervix to the upper genital tract.

## Investigations and clinical decisions

It is most important to exclude ectopic pregnancy by testing urine for  $\beta$  human chorionic gonadotrophin with a sensitive pregnancy testing kit (if available).

Other immediate investigations that should be carried out include dipstick urinalysis to exclude urinary tract infection. If this is positive, a midstream urine sample should be sent for microscopy and culture. The appropriate specimens should be collected for *Chlamydia* nucleic acid amplification testing and gonorrhoea culture. These results will not be available immediately, so treatment needs to be started if the healthcare professional suspects acute PID.

If the woman is seen at a genitourinary medicine (GUM) clinic, immediate microscopy can exclude bacterial vaginosis and may show gonorrhoea infection, but, again, treatment is started once the clinical diagnosis is made.

In a hospital setting, a full blood count, blood chemistry, and blood cultures should be carried out in all patients with high fever or acute abdominal pain with peritonitis. Ultrasonography can identify adnexal disease and exclude ectopic pregnancy in a woman with a positive pregnancy test.

Clinical symptoms and signs of PID only have a 65% positive predictive value when compared with laparoscopy. The routine use of diagnostic laparoscopy to diagnose acute PID, however, is limited by the risks and cost of this procedure. Laparoscopy usually is carried out only in patients in whom the diagnosis remains uncertain.

## Treatment of acute PID

Treatment should be started immediately to reduce the risk of long term sequelae. In the United Kingdom, the incidence of gonorrhoea and genital chlamydial coinfection has increased over the past decade; therefore, the antibiotic regimen used to treat PID should cover *N gonorrhoea*, *C trachomatis*, and anaerobic infections. There may be local variations in *N gonorrhoea* antibiotic sensitivities, and the local microbiology laboratory should be able to advise on appropriate antibiotic choices. When prescribing for women it is important to check

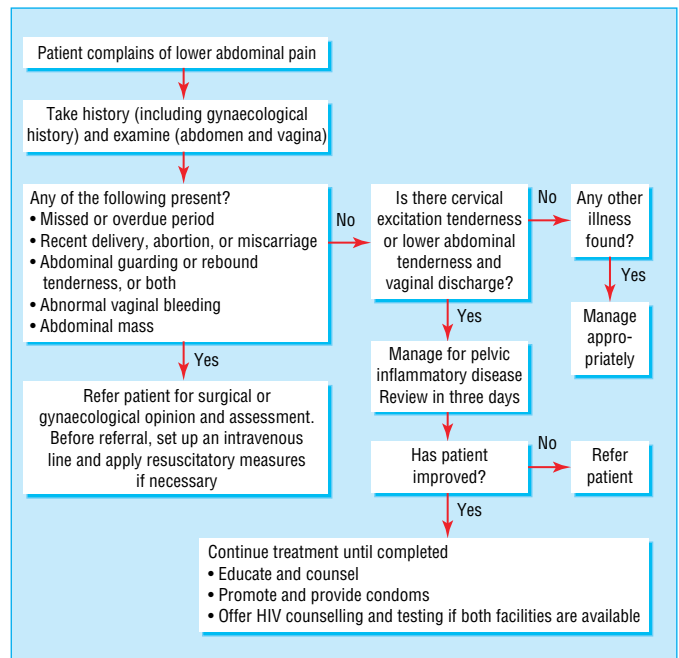
### Oral antibiotic regimens

- Ofloxacin 400 mg twice daily for 14 days (U and C)
- Metronidazole 400 mg twice daily 14 days
- or
- Doxycycline 100 mg twice daily 14 days
- Metronidazole 500 mg twice daily 14 days
- Ceftriaxone 250 mg intramuscular stat
- or
- Amoxyl 3 g orally with 1 g probenecid CW + E

Where these specified antibiotics are not available, the alternative regimen is used. It should

- Cover *N gonorrhoeae* according to local known antibiotic sensitivities
- Include appropriate treatment for 14 days to cover *C trachomatis* and anaerobic bacteria

In pregnancy, erythromycin 500 mg twice daily for 14 days should be used as an alternative to doxycycline. If a long acting preparation is not available four times daily dosing is required



Lower abdominal pain flow chart

### Indications for hospital admission for women with acute PID

- Uncertain diagnosis
- High fever and rigors with dehydration
- Diffuse peritonism
- Adnexal mass
- HIV positive women with immunosuppression if pelvic abscess suspected
- Intravenous drug users if poor treatment compliance and social circumstances
- Intercurrent medical illness, for example sickle cell disease, insulin dependent diabetes mellitus



Adhesions over liver capsule associated with perihepatitis in chlamydial pelvic infection



## ABC of Sexually Transmitted Infections

the risk of early pregnancy, current combined oral contraception use, and any history of antibiotic allergies.

### Further management

The woman should be advised to return for review two or three days after taking oral treatment if her symptoms are no better. If the symptoms have worsened during this time, she should be advised to visit the emergency department.

No evidence supports the routine removal of the intrauterine contraceptive device (IUCD) in acute PID; however, removal should be considered if no clinical response to treatment is seen. In such situations, oral emergency contraception may be required.

The patient must be advised to complete the full course of antibiotics, abstain from sexual intercourse, and attend the GUM clinic for a follow up appointment.

Admission to hospital will allow intravenous antibiotic therapy and fluid rehydration, provision of adequate analgesia, and regular clinical review of symptoms and signs.

Indications for laparotomy in acute pelvic infection include generalised peritonitis, bilateral or enlarging abscess and where the clinical condition has not improved or has deteriorated after 48 hours on intravenous antibiotics.

Recommended parenteral treatment regimens include cefoxitin with doxycycline and a combination of clindamycin with gentamicin when a tubo-ovarian abscess is present.

### Partner notification and aftercare

Partner notification and epidemiological treatment is essential to prevent reinfection, with the consequent increase in long term sequelae.

Women with negative STI test results should be advised that their diagnosis is non-specific PID and that because of the risks of sequelae, doctors have a low threshold for starting antibiotic treatment in sexually active women. Partner notification and epidemiological treatment is still necessary because the male partner may have non-specific urethritis.

Many women will express anxieties over future fertility and may even request tests for tubal patency; however, these tests should only be done in the course of formal investigation after a period of involuntary infertility. It is important to emphasise the need for continued contraception to avoid unplanned pregnancy.

### Prevention of pelvic infection

Management of the complications and reproductive sequelae of *Chlamydia* infection in women costs national health programmes millions each year.

The introduction of screening programmes for genital *C trachomatis* infection has reduced substantially the incidence of acute PID and ectopic pregnancy. Screening programmes are cost effective when the local prevalence rate is 6% and a nucleic acid amplification diagnostic test assay is used.

Studies have shown that bacterial vaginosis is common in women attending for legal abortion and, if left untreated, it is associated with an increased risk of post-abortion pelvic infection. Prophylaxis and treatment for bacterial vaginosis is metronidazole (1 g suppository given rectally at time of operation).

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### Adverse sequelae of PID

#### Chronic PID

The risk of developing chronic PID increases with each episode of acute PID. Chronic pelvic infection is a debilitating condition, with general malaise and fatigue, that results in frequent time off work and incapacity. Symptoms include irregular menses with congestive dysmenorrhoea, secondary deep dyspareunia, chronic pelvic pain, and low backache. Women with chronic PID have increased hysterectomy rates.

#### Tubal factor infertility (TFI)

The risk of TFI increases with each episode of acute infection

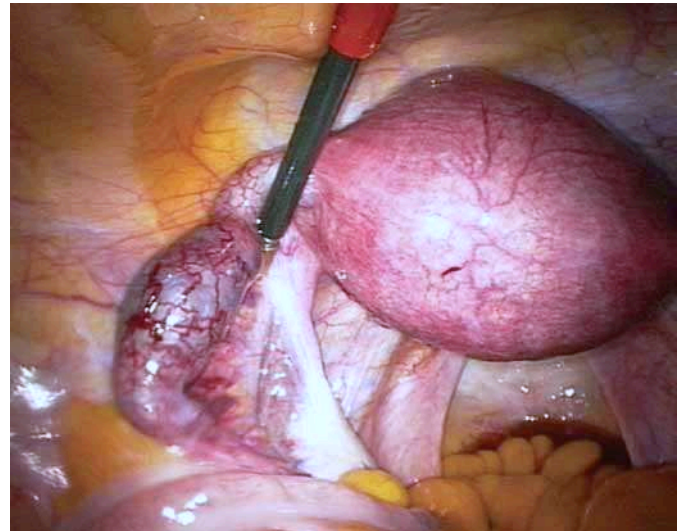
- one episode 12% risk of TFI
- two episodes 35% risk of TFI
- three episodes 70% risk of TFI

95% of infertile women with a history of PID will have TFI and 30% of women with no history of PID will also have TFI, probably as a result of "silent" subclinical infection

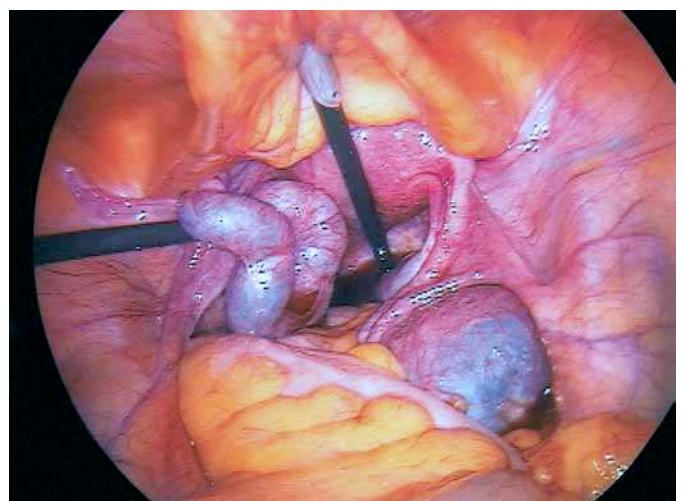
#### Ectopic pregnancy

Ectopic pregnancy can be life threatening. The risk of ectopic pregnancy is 1:100 of all pregnancies, which is increased sevenfold after acute PID

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Laparoscopic view of ectopic pregnancy



Blocked tube at laparoscopy

Evidence also shows that antibiotic prophylaxis effective against bacterial vaginosis given before total abdominal and vaginal hysterectomy prevents post-operative vaginal vault infection.

Although PID can occur after the insertion of an IUCD no evidence at present recommends routine screening or antibiotic prophylaxis for bacterial vaginosis before insertion of the device. Bacterial vaginosis does not affect conception rates during in vitro fertilisation procedures, but it is an independent risk factor for subsequent miscarriage.

The photograph of mucopurulent cervical discharge with cervicitis is the copyright of Dr Marc Steben, Clinique de l'Ouest, Montreal, Canada. The photographs of adhesions over the liver capsule and the ectopic pregnancy are courtesy of Mr Alfred Cutner

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### Opportunities for *Chlamydia* screening to prevent pelvic infection\*

All women and men

- Younger than 25 years
- Older than 25 years with a new sexual partner or two or more partners in the previous year
- Of any age with symptoms
- Attending GUM clinics

All women

- Younger than 35 years before surgical uterine instrumentation—for example, hysteroscopy
- Before IUCD insertion
- Before induced abortion (termination of pregnancy)

\*British guidelines from Chief Medical Officer and Royal College of Obstetricians and Gynaecologists

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# 9 Sexually transmitted infections in pregnancy

Helen Mitchell

Pregnant women may be unaware they have an existing asymptomatic sexually transmitted infection (STI) or they may be still at risk of acquiring an STI during pregnancy. Therefore, it is necessary to overcome a natural hesitancy to discuss risk factors for STIs. Infections at this time can affect the fetus and neonate by vertical transmission, which may result in serious and life threatening consequences. Screening for infections in pregnancy and starting early treatment can prevent adverse outcomes for the mother and neonate.

The management of STIs in pregnancy should be guided by expert advice because certain treatments are contraindicated during pregnancy. A test of cure should be carried out after treatment and before delivery for women testing positive for *Chlamydia trachomatis*, *Trichomonas vaginalis*, and *Neisseria gonorrhoeae*.

## Gonorrhoea

### Mother

Uncomplicated gonorrhoea rates in young women have increased dramatically over the past decade in the United Kingdom. Worldwide gonorrhoea prevalence varies, with particularly high rates reported in Africa.

### Baby

Intrapartum infection occurs in about 30-50% of babies born to untreated mothers and is associated with

- Conjunctivitis (ophthalmia neonatorum) “sticky eye” with onset of purulent conjunctival discharge between two and five days after birth
- Disseminated neonatal infection
- Diagnosis is by Gram stained smear and culture of conjunctival swab.
- Treatment of established infection is with systemic antibiotics, for example ceftriaxone.

## *C trachomatis*

### Mother

Genital chlamydial infection rates in young women have also increased substantially in the United Kingdom. Non-invasive testing for chlamydia using nucleic acid amplification tests, for example polymerase chain reaction (PCR) on self taken vulval-introital swabs, may be appropriate in late pregnancy and in situations in which the woman declines a speculum examination.

### Baby

Intrapartum infection in babies born to untreated mothers is associated with

- Conjunctivitis (ophthalmia neonatorum) in 30-50% of babies with onset occurring 3-14 days after birth
- Otitis media
- Nasopharyngitis

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## Screening in pregnancy guidelines

### Routine antenatal screening

- In the United Kingdom the current programme includes serology for syphilis, Hepatitis B, and HIV antibody testing with a pre-test discussion

### Hepatitis C

- Screening for anti-hepatitis C virus (anti-HCV) antibodies should be done in high risk groups, such as intravenous drug users and women that received organ transplant or blood transfusion before HCV screening commenced

### Other STIs

- Screening for gonorrhoea, chlamydia, and *T vaginalis* in pregnancy should be considered in women with STI risk factors, young women under 25 years and those with a history of STIs or pelvic inflammatory disease, or both.
  - Routine antenatal screening for gonorrhoea and chlamydia to prevent complications of maternal infection in pregnancy and neonatal infection is appropriate in high prevalence countries
  - No evidence currently supports routine antenatal screening using type specific antibody testing for herpes simplex virus (HSV-1 and HSV-2)
- 

**Partner notification and epidemiological treatment is essential to prevent reinfection during the antenatal period and further risk of vertical transmission**

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## Gonorrhoea

Gonorrhoea in pregnancy is associated with

- Low birth weight
- Premature delivery
- Pre-term rupture of membranes
- Chorioamnionitis
- Postpartum sepsis
- Secondary infertility

Appropriate treatment regimes include a single intramuscular dose of ceftriaxone (250 mg), cefotaxime (500 mg), and spectinomycin (2g) (see Chapter 5). Ciprofloxacin and tetracyclines should be avoided in pregnancy.

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## *C trachomatis*

*C trachomatis* in pregnancy is associated with

- Low birth weight
- Premature delivery
- Pre-term rupture of membranes
- Chorioamnionitis
- Postpartum sepsis

Treatment in pregnancy is with erythromycin (500 mg twice daily) for two weeks or amoxicillin (500 mg three times daily) for seven days. Doxycycline and tetracycline are both contraindicated in pregnancy

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- Chlamydial pneumonitis, which presents with staccato cough, tachypnoea, and failure to thrive, occurs after 4-12 weeks in 10-20% of exposed babies.

Diagnosis is by culture of *C trachomatis* or nucleic acid test (NAAT) on conjunctival, nasopharyngeal, and rectal swabs. Treatment of established infection is with systemic antibiotics, for example erythromycin.



Chlamydial pneumonitis

## Genital herpes simplex infection

### Mother

The diagnosis of genital herpes simplex infection (HSV-1 and HSV-2) in women has seen a slow but steady increase and about 5% of antenatal attendees in the United Kingdom have a history of symptomatic genital herpes. On serological testing, 25% of genitourinary medicine clinic attendees and 20% of adult Americans have type specific antibodies to HSV-2. However, only 35% of infected adults are aware that they have genital herpes.

Maternal primary HSV infection during pregnancy is associated with

- Spontaneous abortion
- Low birth weight
- Premature delivery
- Stillbirth.

It is important to ascertain whether a pregnant women presenting with genital ulceration has a recurrent infection or a true primary HSV infection. In tropical countries it is important to exclude other causes of genital ulceration (see Chapter 11).

Differentiation of primary from non-primary infection is by serology because history is a poor indicator. Seroconversion in primary infection takes between three and six weeks and can be tracked using immunoglobulin G and immunoglobulin M type specific antibody testing.

### Ophthalmia neonatorum

- Ophthalmia neonatorum is conjunctivitis that develops within 21 days of birth. In the United Kingdom it is a notifiable condition
- Chlamydial or gonococcal infection should always be excluded. Chlamydial ophthalmia is more common but it is not possible to distinguish them clinically
- Untreated gonococcal ophthalmia neonatorum can lead to corneal ulceration and perforation with permanent loss of vision
- Diagnosis is by Gram stained smear and culture of a swab from the conjunctiva for *N gonorrhoea*, culture for *C trachomatis*, and ligase chain reaction
- Established infection is treated with systemic antibiotics
- In areas of high STI prevalence without routine antenatal screening ocular prophylaxis should be given routinely to all newborn babies within one hour of birth, using a 1% tetracycline or 0.5% erythromycin eye ointment
- Prophylactic systemic ceftriaxone should be considered for babies born vaginally to mothers with known untreated gonorrhoea



Ophthalmia neonatorum

### Advice for pregnant women with known recurrent genital herpes

- Women with recurrent genital herpes can deliver vaginally if they do not have overt genital ulcers at the time of delivery
- Repeated viral cultures during pregnancy are of no clinical value in predicting recurrences or viral shedding at the time of delivery
- Women with a recurrence at the time of delivery are currently delivered by lower segment caesarean section to prevent intrapartum viral transmission
- If recurrent lesions are present at the time of delivery there is a low risk of neonatal herpes even with vaginal delivery. This risk must be offset against the maternal risks of surgical delivery and some obstetricians may agree to vaginal delivery after discussion with the pregnant woman to obtain her informed consent
- Suppression therapy during the third trimester may reduce the risk of recurrence at the time of delivery in women with frequent recurrence but this does not reduce viral shedding so the benefit is uncertain

# ABC of Sexually Transmitted Infections

Women presenting with suspected primary genital herpes acquired during the third trimester of pregnancy should be offered aciclovir antiviral treatment and delivered by elective lower segment caesarean section if labour commences within a six week period after diagnosis.

The risks of primary HSV-2 are highest in the last trimester and if, during this time, the male partner has an episode of recurrent genital HSV-2 sexual intercourse should be avoided.

## Baby

Antepartum HSV transmission is rare and may cause stillbirth. Neonatal HSV infection is rare in the United Kingdom and the United States (2 per 100 000 and 7 per 100 000 live births, respectively). The highest risk of intrapartum transmission and neonatal infection is 40% for babies born by vaginal delivery in a woman with primary genital herpes infection at the time of delivery. In women with recurrent herpes at vaginal delivery the risk of neonatal herpes is less than 1%. Postnatal infection can occur if a relative or caregiver with a herpetic whitlow or orolabial HSV-1 handles or kisses the child.

Confirmation of diagnosis is essential and the method used will depend on the laboratory services available from EM of vesicle fluid to viral PCR testing.

## HIV

### Mother

By the end of 2002 an estimated 42 million adults and children worldwide are living with HIV and 50% of infected adults are women. In some of the countries in Sub-Saharan Africa one in three women attending antenatal services will be HIV positive.

In the United Kingdom, data obtained by national unlinked anonymous monitoring of HIV infection show that one in 200 women attending antenatal clinics in Central London are HIV positive, but in rural areas only one in 2500 women are HIV positive. During 2002, 720 births took place to HIV positive women in the United Kingdom, of which 80% were to previously diagnosed women.

Worldwide, HIV in pregnancy is associated with

- Low birth weight
- Premature delivery
- Stillbirth.

Pregnancy does not seem to have an adverse effect on the health of an HIV positive woman or her long term prognosis unless she has AIDS or a concurrent infection, such as tuberculosis.

### Baby

Each day 2000 children in Africa are newly infected with HIV and many millions of children have been orphaned by HIV. The risk of mother-to-child transmission is related to the maternal viral load, stage of HIV disease, duration of pregnancy at the time of delivery and the risk is increased by vaginal delivery.

The highest transmission rates occur in resource poor countries with high HIV prevalence where interventions to prevent transmission are not widely available. The additional risks of transmission in resource poor countries include breast feeding after delivery. In some societies, bottle-feeding is associated with social stigma and a substantial risk of infant death from acute gastroenteritis.

All babies born to infected mothers will exhibit maternal HIV antibodies; in uninfected babies 50% will lose the antibodies by 10 months. All uninfected babies should be confirmed as HIV negative at six months using HIV PCR testing and at 18 months by serial antibody titre.

**Pregnant women should be informed of the risks of acquiring HSV infection during pregnancy. Receptive oral sex with a partner with orolabial HSV-1 is a risk factor for women with no personal history of orolabial or genital herpes infection.**

**Neonatal herpes simplex infection can be localised or disseminated affecting multiple organs, including hepatitis and encephalitis. If neonatal HSV is suspected immediate intensive treatment with intravenous antiviral therapy should be started. Disseminated infection has a high mortality rate (70%) even with effective antiviral therapy. Surviving neonates are at a high risk of neurological sequelae.**

### HIV testing in pregnancy

- All pregnant women should be offered HIV screening routinely by HIV antibody testing with a pre-test discussion
- Women may not be able to accurately assess their personal risk of HIV infection
- The universal offer of HIV testing in pregnancy that allows women to opt out is more effective than selective offer or allowing women to choose if they feel HIV testing is necessary
- The medical benefit of knowing a women's HIV status is that women who test positive can be offered interventions that effectively reduce the risks of vertical transmission of HIV
- Mother-to-child transmission without interventions during pregnancy is 15-30%, which is further increased by breast feeding
- The transmission risk can be effectively reduced to less than 1% by the following interventions during pregnancy

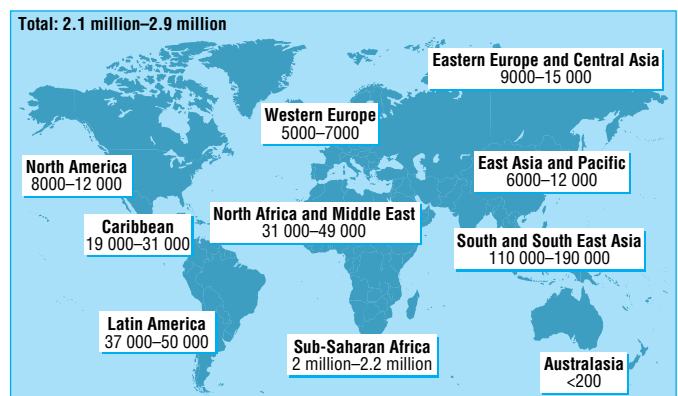
Antiretroviral therapy for the mother which includes zidovudine or nevirapine. Strong evidence shows that both treatments effectively reduce the risk of vertical transmission

Elective caesarean section delivery

Avoiding breast feeding

Antiretroviral therapy for the neonate after delivery

- In high prevalence countries women should be retested in the third trimester



Number of children (younger than 15 years) estimated to be living with HIV and AIDS as of end 2003. Adapted from www.UNAIDS.org

## Syphilis

### Mother

Worldwide, syphilis (*Treponema pallidum*) is still a common infection in pregnancy. The rates are low in the United Kingdom; nevertheless, routine antenatal screening is still carried out. In high prevalence countries congenital syphilis can occur as a result of acquisition in late pregnancy and infected women not attending for antenatal care. The treatment regimen used in pregnancy depends on the stage of maternal infection, history of antibiotic allergy and is usually with intramuscular benzathine penicillin injections. Effective maternal treatment will prevent congenital syphilis in the unborn child except when treatment has commenced late in the third trimester.

### Baby

Syphilis is associated with 25% of stillbirths in rural Sub-Saharan Africa and congenital syphilis accounts for 30% of perinatal deaths. The risk of congenital syphilis in untreated cases is related to the stage of maternal syphilis with the risk decreasing with advancing stage of maternal disease. Up to 50% of babies born to mothers with untreated primary or secondary infection will be infected compared with less than 5% of babies born to mothers with late latent infection.

Transplacental transfer of maternal antibodies occurs but if the baby is not infected the treponemal antibody will be lost by six months. Diagnosis of congenital infection occurs by demonstrating the presence of treponemes in lesions and by serology using the fluorescent treponemal antibody absorption test for immunoglobulin M. Treatment of an infected neonate is with intravenous penicillin.

## Hepatitis B

In the United Kingdom the prevalence of hepatitis B carriage in the antenatal population is low. In women from endemic areas carriage is higher and vertical transmission can occur, especially when the mother is hepatitis Be antigen positive.

Parental consent for immunisation should be obtained before birth so that babies born to high risk carriers can be given hepatitis B virus immunoglobulin passive vaccination and active immunisation shortly after birth to prevent both neonatal infection and the risk of chronic carriage.

## Hepatitis C

The risk of vertical transmission with hepatitis C is estimated to be 6%. Transmission may be increased in co-infection with HIV. No specific intervention has been identified to reduce the transmission rate.

## Genital warts

Genital warts may appear for the first time or increase in size and number during pregnancy as a result of changes in local cellular immunity. There is a very small risk of vertical transmission resulting in neonatal laryngeal, mucous membrane, or genital human papillomavirus infection. Imiquimod, podophyllin, and podophyllotoxin topical treatments are all contraindicated in pregnancy.

## *T vaginalis*

Trichomonae infection in pregnancy is associated with adverse pregnancy outcomes, including pre-term delivery and low birth

### Clinical features of congenital syphilis

Early congenital syphilis is a multi-organ disease that can present with hepatosplenomegaly

- Anaemia
- Petechiae
- Periostitis

Latent (early and late)

- No clinical signs of active infection

Late (more than two years is similar to adult late disease)

- Osteoperiostitis
- Joint effusions usually knees—Clutton's joints
- Gummata
- Neurological and cardiovascular complications

The lesions of early and late syphilis may heal but result in classical stigmata of congenital syphilis

- Sabre shaped tibial deformity
- Saddle nose deformity
- Frontal bossing of the skull
- Linear scars around the mouth
- Small notched incisors
- Corneal opacities



Congenital syphilis on teeth



Congenital syphilis on mouth

## ABC of Sexually Transmitted Infections

weight. Pregnant women can be treated with oral metronidazole treatment regimes but high dose metronidazole treatment regimes should be avoided in the first trimester and also during breast feeding because they may cause breast milk to taste bitter to the infant.

### Bacterial vaginosis

At present, no evidence supports routine antenatal screening for bacterial vaginosis for all pregnant women or that treating asymptomatic women with bacterial vaginosis in general antenatal clinics reduces their risk of pre-term labour. However, some evidence shows that treating bacterial vaginosis reduces pre-term labour in women with a history of pre-term delivery and it may be that this subgroup of women could benefit from early screening and oral treatment. Further trials are needed to show that such screening and antenatal treatment reduces perinatal mortality and morbidity. Symptomatic pregnant women should be treated with oral metronidazole (400 mg twice daily) for between five and seven days.

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#### Further reading

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The photograph of ophthalmia neonatorum is reproduced from King A, Nicol C. *Venereal diseases*. London: Baillière Tindall, 1969

# 10 Other conditions that affect the female genital tract

Helen Mitchell

## Bartholin's gland conditions

The Bartholin's glands can become enlarged by abscess or cyst formation. In abscess formation, common infecting pathogens include *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Escherichia coli*,  $\beta$  haemolytic streptococci, *Staphylococcus aureus*, and anaerobes.

### Investigations

All sexually active patients who present with a cyst or abscess should be offered a full sexually transmitted infection (STI) screen. However, if the client is too uncomfortable for an examination, the screen can be deferred until follow up. If the abscess is discharging pus, additional swabs of pus should be taken for microscopy, culture, and sensitivity.

## Vulvar symptoms

Women may present with complaints of genital skin itching, burning, soreness, and discomfort during sexual intercourse. Some women experience longstanding symptoms and despite frequent clinic attendances may fail to receive a diagnosis and appropriate advice or treatment with consequent psychological and psychosexual morbidity. In some women, relationship difficulties, psychosexual problems, and depression can lead to somatisation and genital symptoms with no clinically apparent cause.

### Clinical management

A detailed history is very important and should include onset and duration of symptoms and whether any topical treatments have been used and with what degree of success.

Details of personal habits and hygiene should be covered, such as use of perfumed soaps, bath additives, douching, depilatory preparations, alternative remedies, laundry detergents, and fabric conditioners. If the patient admits to scratching, ask whether this is worse at night and if they regularly wear fingernail varnish, because this can contain formaldehyde, which is a contact irritant. A personal and family history of atopy, asthma, hayfever, eczema, other dermatological conditions, and nickel and food allergies can be relevant.

### General principles

- The external genital area should be examined carefully. The skin of the rest of the body, scalp, mouth, eyes, and fingernails may need to be examined as appropriate. The inguinal lymph nodes should be palpated and the vaginal mucosa inspected by speculum examination
- Vulvar symptoms often are caused by recurrent vulvovaginal *Candida* infection
- If symptoms persist and tests for STIs and other genital infections are negative, it is important to consider whether there is an underlying dermatological disorder
- Scratching and rubbing to relieve symptoms can result in both secondary skin changes and infection that can further alter the clinical appearances
- Vulvar skin biopsy may be required to make a definitive diagnosis
- Referral to specialist services with the combined clinical expertise of a dermatologist, gynaecologist, or genitourinary medicine physician should be considered for all women with persistent vulvar symptoms

**A Bartholin's cyst is a painless enlargement that may increase or decrease in size over time, and the history is often longer or intermittent**

**A Bartholin's abscess is a painful genital swelling and on examination the gland is tensely enlarged with pain, local redness, and warmth. The swelling may become fluctuant "pointing" and will eventually discharge pus, after which the intense throbbing pain is relieved**



Discharging Bartholin's abscess. Reproduced from King A, Nicol C. *Veneral diseases*. London: Baillière Tindall, 1969

## Management of Bartholin's gland conditions

### Abscess

- Painful non-discharging abscess—refer urgently to on call gynaecology for a marsupialisation or incision and drainage procedure
- Abscess has spontaneously discharged and pus is weeping freely—oral flucloxacillin (500 mg four times daily orally) should be prescribed for five days. Refer the patient to routine gynaecology outpatients because recurrence is common and may require interval marsupialisation
- Advise rest, loose clothing, and analgesia as required, for example, ibuprofen
- Use Sitz baths (one cup of salt in bowl of water) and cotton balls to gently clear away pus
- Pat the area dry after washing or dry with a hairdryer on a low heat setting
- Follow up appointment for results or to perform full STI screen

### Cyst

- Offer full STI screen
- No antibiotics are required
- Referral to routine gynaecology outpatient appointment to consider interval marsupialisation

## Common causes of vulvar symptoms

- Genital infections
- STIs
- Vulvodynia
- Genital dermatoses
- Psychosexual problems



## Vulvar and perianal itching

Threadworm infestation should be considered if the itching is predominately perianal (pruritus ani) rather than vulvar (pruritus vulvae). A “sticky tape” test should be carried out by applying a clear sticky tape strip to the perianal skin in the morning before washing. The tape is applied to a glass microscopy slide and examined for threadworm ova.

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### General advice for patients with vulvar symptoms, including genital itching

- Aqueous cream can be used as a soap substitute for washing
- A bland emollient is useful as a skin moisturiser
- Avoid perfumed products, bath additives, talcum powder, vaginal deodorant sprays, and sanitary pads with perfume or deodorisers
- Change laundry detergent to a skin sensitive brand or a non-biological brand
- Do not use fabric conditioner for undergarments
- Shaving or use of depilatory creams in the genital area may exacerbate symptoms
- Patients sensitive to spermicide or latex condoms can try using washed latex condoms or those with only a lubricant
- Perfumed oils and creams should not be used as lubricants
- Avoid self treatment with over the counter or alternative remedies
- Try not to scratch because this can damage the skin and set up a cycle of itch-scratch-itch, which then needs to be broken by using a moderate potency topical steroid initially then reducing the dose as symptoms resolve
- A tepid bath, ice pack, or cold soaked cotton pad applied locally may help reduce an intense need to scratch
- Itching can often be worse at night. A mildly sedating antihistamine, such as chlorpheniramine, at night may help reduce nocturnal scratching

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## Genital dermatoses

### Lichenification

This can occur in any itchy skin condition and describes the appearance where the skin is thickened and pale with accentuated skin line markings and folds. When scratching is marked, evidence of excoriation with areas of broken skin and traction hair loss will be seen. Post-inflammatory hypopigmentation and hyperpigmentation can be present.

### Irritant contact dermatitis

This is commonly caused by skin sensitisers present in products used in general and genital hygiene. Avoidance of some common contact irritants may relieve symptoms.

### Allergic contact dermatitis

This can occur with self treatment with essential oils, local anaesthetic creams, and pile relieving ointments common in patients with chronic symptoms. Contact dermatitis medicamentosa is an allergic contact dermatitis usually caused by excipients or additives in topical treatment.

Patch testing may be useful for identifying specific allergens in atopic eczema and allergic contact dermatitis. Nickel allergy is a form of allergic contact dermatitis and may be relevant in women with poor quality genital piercings.



Non-specific vulvar appearance with oedema, redness, and introital splitting

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### Causes of genital itching

#### Infection

- Candidiasis
- *Trichomonas vaginalis*
- Genital warts
- Genital herpes simplex
- Molluscum contagiosum

#### Infestation

- Pediculosis pubis (crab lice)
- Threadworms

#### Genital dermatoses

- Non-allergic contact or irritant dermatitis
- Eczema
- Psoriasis
- Lichen sclerosus
- Lichen planus
- Seborrhoeic eczema

#### Neoplastic conditions

- Pre-malignant intraepithelial neoplasia
- Invasive neoplasia

#### Systemic conditions

- Diabetes mellitus
- Renal or hepatic dysfunction



Hyperpigmentation secondary to contact dermatitis caused by the use of depilatory creams in the genital area

**Psoriasis**

The appearance of affected genital areas may be altered, with red, glazed, well defined patches that are often not scaly. It is important to examine the limb flexures for characteristic “silvery” plaques and the nails for pitting.

**Eczema**

The characteristic appearance of eczema can be altered on the vulva because it is a moist area prone to friction from clothing and during sexual intercourse. Other skin sites may be affected and there may be a personal or a family history of atopy, such as hayfever and asthma.

**Seborrhoeic eczema**

This can affect the vulva and also may be evident on the face, chest, scalp, and eyebrows. It is treated with a mild steroid containing an antifungal component.

**Lichen simplex chronicus**

Plaques of lichenification are seen in this condition, but it is not a specific diagnosis. It is important to review the skin appearance once symptoms are controlled by a topical steroid to exclude an underlying dermatosis, particularly lichen sclerosis.

**Lichen sclerosis**

Lichen sclerosis is an autoimmune condition linked with alopecia areata and vitiligo. There may be predisposing genetic factors and, in some cases, infective trigger agents. Lichen sclerosis can occur at any age and affects both sexes, but is most common in women over 50 years of age.

The anogenital area is commonly affected in a classic figure of eight distribution around the vulva and anus. Common presenting symptoms are itching, soreness, dyspareunia, and painful fissures at the introitus. The affected skin is dull and white, with horizontal skin wrinkling, telangiectasia, and small ecchymoses. In chronic, untreated cases, loss of normal anatomy may result with fusion of the clitoral hood, abnormal clitoral sensation, resorption of the labia minora, and narrowing of the introitus.

Diagnosis can be made clinically in overt cases or by skin biopsy that shows characteristic histological appearances.

Treatment is with a potent topical steroid twice daily until symptoms resolve and the condition is quiescent. Maintenance treatment continues with weekly or fortnightly applications.

The lifetime risk of squamous cell carcinoma in lichen sclerosis is 4-5% and women should be taught how to examine themselves and when to seek medical attention, for example for ulceration, raised lesions, and localised persistent symptoms.

Surgical treatment is indicated rarely but may be useful when introital narrowing precludes satisfactory sexual intercourse.

**Lichen planus**

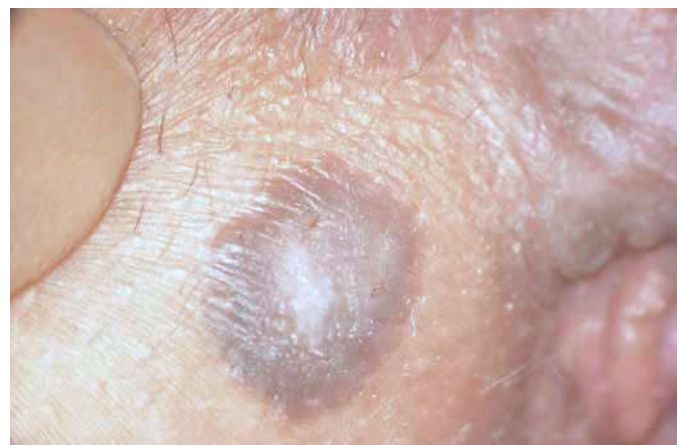
Lichen planus is considered to be an autoimmune disorder that affects skin or mucosal surfaces, or both. Women may present with pruritus and dyspareunia with associated oral symptoms. The classical appearances are itchy, purple papules or plaques on the vulva, which can be white or have post-inflammatory hyperpigmentation. These lesions may exhibit Köebnerisation with local extension along trauma and scar lines. Wickham’s striae is a lacy white appearance on the surface of the affected genital mucosa and may also be identified on the flexor aspects of the wrists, gingival margins, and oral mucosa.



Early stages of lichen sclerosis in a young woman, affecting the labia minora on left



More advanced lichen sclerosis with loss of architecture and marked pallor with telangiectasia



Suspicious lesion with pigmentation that should be referred for expert opinion and histological diagnosis

**Malignant melanoma is the second most frequent vulvar malignancy, and it is important to refer any patient with a suspicious pigmented genital lesion for an expert opinion to exclude pre-malignant or malignant change**

# ABC of Sexually Transmitted Infections

Clinical findings are important to establish the diagnosis because the histological appearances on skin biopsy often show only non-specific inflammatory changes.

Treatment is with topical steroids. In vulvovaginal gingival syndrome, the vagina is also affected with painful red erosions, and consequent synechiae formation can distort the vaginal anatomy, causing severe dyspareunia. In such cases, systemic and topical intravaginal steroids are necessary.

## Pigmentary changes

Areas of pigmentation change may be seen on examination, and it is important to ascertain whether any localised symptoms are present.

- Lentiginosities are areas of darker pigmentation caused by a localised increase in melanocytes
- Post-inflammatory hypopigmentation and hyperpigmentation can occur in women with chronic itching area with well circumscribed areas of depigmentation and scratching
- Vitiligo is an autoimmune skin condition with well circumscribed areas of depigmentation that can involve the genital area.

## Vulval intraepithelial neoplasia and invasive vulval neoplasia

Vulval intraepithelial neoplasia (VIN) can be low grade (VIN I) or high grade (VIN II/III). Pre-malignant lesions in the genital area can be difficult to identify clinically because there are no consistent diagnostic features, and VIN can be warty or flat, single or multiple, asymptomatic or symptomatic, and varied in coloration.

Squamous cell carcinoma is responsible for 90% of all vulvar malignancies and is associated with the presence of a high risk human papillomavirus (for example, types 16, 18, 33, and 35).

Specialist advice is recommended for persistent genital skin lesions and genital warts that do not respond to topical treatment. Urgent referral is required for suspicious lesions with ulceration, bleeding, or dark or patchy pigmentation.

## Vulval pain syndromes

Vulval pain can be caused by local infection, trauma, topical wart treatments, and pelvic floor disorders, and can occur in association with systemic disease. Vulvodynia is defined by the International Society for the Study of Vulvovaginal Disease (ISSVD) as chronic burning, soreness, or rawness. Vulvodynia has features in common with other pain syndromes and psychological support and psychosexual counselling are important in long term management.

Vulvar vestibulitis syndrome is a triad of symptoms and signs with superficial dyspareunia on attempted penetration or tampon insertion, erythema, and point tenderness localised in the vestibule. The aetiology is uncertain, and it is thought to be a self limiting condition. Approaches to treatment include general vulvar symptoms advice, topical local anaesthetic, and lubricants to facilitate sexual intercourse.

Cyclical vulvodynia occurs when recurrent vulval symptoms happen in relation to menstruation and coitus. It may be caused by changes in vaginal pH or associated vulvovaginal candidiasis and bacterial vaginosis. Intravaginal azole treatment at the cyclical trigger points may be beneficial.



Suspicious lesion with variable pigmentation (VIN III) that should be referred for expert opinion and histological diagnosis



Red raised suspicious lesion (squamous cell carcinoma) that should be referred urgently for expert opinion and histological diagnosis

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### ISSVD classification of vulval pain syndromes

- Vulvar vestibulitis (provoked localised vulval dysaesthesia or vestibulodynia)
  - Cyclical vulvodynia
  - Dysaesthetic vulvodynia (unprovoked generalised vulval dysaesthesia)
  - Vulvar dermatoses
  - Vulvar papillomatosis
- 



Vulvar papillomatosis with characteristic club shaped papillae

Dysaesthetic vulvodynia is characterised by a history of diffuse and constant burning pain and affects an older age group of women. This condition has closer parallels with glossodynia and is thought to be a disorder of cutaneous sensory perception. Treatment is with tricyclic antidepressants or the newer antiepileptic drugs, for example gabapentin.

Vulvar papillomatosis describes the appearance of small lobular papillae on the inner surface of the labia minora and around the vestibule. These papillae now are thought to be a normal anatomical variant, and in most women are asymptomatic and do not require treatment.



Localised redness in the vestibule with associated point tenderness elicited using a cotton tip swab

## Psychosexual problems

Chronic vulvovaginal symptoms can interfere seriously with sexual and emotional relationships, resulting in reduced libido and avoidance of sexual intercourse if it exacerbates symptoms. Psychosexual problems can occur after an acute STI diagnosis or recurrent episodes of genital herpes or vaginal discharge.

Repeat clinic attendances by a woman complaining of abnormal vaginal discharge or vulvar symptoms with no apparent physical cause may be a covert way for the woman to raise concerns or feelings about their genital area. Therefore, it is important that all doctors are able to recognise psychosexual problems and, where appropriate, offer referral for psychosexual counselling.

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### Causes of dyspareunia

#### Superficial

##### Infection

- Candidiasis, *T vaginalis*, and genital herpes simplex

##### Trauma

- Episiotomy scars, introital fissures, or tears caused by sex toys

##### Vulval disorders

- Lichen sclerosus
- Lichen planus
- Vulval pain syndromes
- Post-menopausal vulvovaginal atrophy
- Iatrogenic self treatment, post-radiotherapy, and 5-fluorouracil

##### Psychosexual

- Vaginismus

#### Deep

- Ovarian disease
  - Endometriosis
  - Acute and chronic pelvic inflammatory disease
  - Uterine fibroids
- 

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# 11 Genital ulcer disease

Frances Cowan

Several sexually transmitted infections (STIs) can affect both sexes and do not differ substantially in their presentation between men and women. The next chapters deal with such infections, namely genital ulceration, genital growths and infestations, hepatitis, HIV, and AIDS.

## Genital ulceration

Genital ulceration (or erosion) is a common symptom in both sexes and may be caused by a sexually transmitted agent, other infectious agents, a dermatological condition, or trauma. Particular points that need to be elicited from the patient to aid diagnosis are the number of ulcers, the time they have been present, the degree of discomfort they cause, and when they appeared in relation to sexual intercourse, trauma, or lesions elsewhere on the body.

### Multiple painful ulcers

Multiple painful ulcers are most commonly caused by the herpes simplex virus (discussed in detail below). The first episode of genital herpes may occur within one to two weeks of infection, but it also may occur some time later. It may be associated with systemic symptoms in addition to ulceration, including fever, headache, myalgia, and urinary or faecal retention (or both). Some people get ulceration at multiple sites (mouth, nipples, and fingers) during their first episode. Occasionally, herpes zoster gives rise to genital ulceration, but recurrent ulceration on the genitals, buttocks, or thighs almost always is caused by herpes simplex infection.

Other infections that can cause multiple painful ulcers or erosions include balanitidis (due to *Candida*, *Trichomonas*, and  $\beta$  haemolytic streptococci) and infestations with scabies or pubic lice (in which the ulceration is secondary to scratching). People (or sexual contacts) who have travelled or live in areas in which chancroid occurs (parts of sub-Saharan Africa, the Americas, and Asia) may have multiple painful ulcers. These ulcers are caused by *Haemophilus ducreyi*, which has a short incubation period of just two to five days.

A number of dermatological conditions can occur on the genitalia (see Chapters 6 and 10) and many of these can cause superficial ulceration or erosions (for example psoriasis,



Chancroid

**Most sexually transmitted causes of ulceration are said to be either “multiple and painful” or “solitary and painless,” although, of course, exceptions exist and it is unwise to make a presumptive diagnosis on the basis of these signs and symptoms alone**

Multiple		Solitary	
<b>Painful</b>	<ul style="list-style-type: none"> <li>Herpes genitalis</li> <li>Herpes zoster</li> <li>Behçet's syndrome</li> <li>Chancroid</li> </ul>	<ul style="list-style-type: none"> <li>Balanitis or vulvitis (<i>Candida</i>, <i>Trichomonas</i>, Vincent's organisms)</li> <li>Erythema multiforme</li> <li>Stevens-Johnson syndrome</li> <li>Folliculitis</li> <li>Furuncle</li> <li>Scabies</li> </ul>	<ul style="list-style-type: none"> <li>Tuberculosis (recurrent herpes genitalis)</li> </ul>
<b>Painless</b>	<ul style="list-style-type: none"> <li>Secondary syphilis</li> </ul>	<ul style="list-style-type: none"> <li>Granuloma inguinale</li> <li>Leukoplakia</li> <li>Lichen sclerosis et atrophicus</li> <li>Balanitis xerotica obliterans</li> <li>Carcinomas</li> </ul>	<ul style="list-style-type: none"> <li>Primary syphilis</li> <li>Gumma</li> <li>Circinate balanitis (Reiter's syndrome)</li> <li>Crohn's disease</li> <li>Carcinoma</li> <li>Trauma</li> <li>Lymphogranuloma venereum</li> </ul>

Causes of genital ulceration and erosions

### Chancroid (soft sore)

#### Cause

- *Haemophilus ducreyi* (Gram negative bacillus)

#### Distribution

- Widespread in tropical countries, occasional outbreaks in large cities in wealthier countries. Large epidemic reported from Greenland

#### Incubation period

- Three to 10 days

#### Main symptoms

- Soft, painful, anogenital ulcers, painful inguinal adenopathy (mostly unilateral). Ulcers single or multiple. Purulent base, contact bleeding, and undermined edge characteristic

#### Complications

- Destructive (phagaedenic) ulceration, inguinal abscess formation

#### Diagnosis

- Usually clinical in endemic areas. Can be confirmed by culture on special media. Polymerase chain reaction tests have been developed

#### Treatment

- Ciprofloxacin: 500 mg orally twice daily for three days (C, E, U, W)
- Ceftriaxone 250 mg intramuscularly in a single dose (C, E, U, W)
- Azithromycin 1 g orally in a single dose (C, E, U, W)
- Erythromycin 500 mg orally four times daily for seven days (E, U, W), three times daily for seven days (C)
- Abscesses—aspiration or incision and drainage indicated for fluctuant lesions
- Resistance—commonly found to co-trimoxazole
- HIV co-infection—treatment failure possible and extended therapy is sometimes required

C= Centers for Disease Control, USA; E=European STI guidelines; U=UK National Guidelines; W= World Health Organization

dermatitis, lichen planus, and drug eruptions). These often but not always are associated with dermatological problems elsewhere. Behçets disease causes genital ulceration that is usually associated with oral lesions.

### Single painless ulcers

The most common cause of painless genital ulceration is primary syphilis (see Chapter 12). The incubation period is usually 21 days, but lesions may show from 9-90 days after sexual intercourse with an infected partner. The gumma that occur in tertiary syphilis are also solitary and painless.

Other causes of solitary, painless ulcers are carcinoma, circinate balanitis, or lichen sclerosus et atrophicus (previously known as balanitis xerotica obliterans). Lymphogranuloma venereum and donovanosis are two tropical STIs that should be considered in people living in or travelling to endemic areas or those who are in sexual contact with people from such areas. Self inflicted trauma (dermatitis artefacta) may result in large, solitary, apparently painless, ulcers.



Behçets disease

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### Lymphogranuloma venereum (LGV)

#### Cause

- *Chlamydia trachomatis*, L1, L2, and L3 serotypes

#### Distribution

- Mainly tropical countries, rare compared with other STIs

#### Incubation period

- Three to 30 days

#### Main symptoms

- Characteristically a very small genital ulcer is the first sign. May also start with urethritis or proctitis. Presentation is most common at the next stage where painful, usually unilateral inguinal adenopathy develops usually with fever and malaise. Untreated patients may subsequently develop discharging inguinal sinuses, genital lymphoedema, fistulas, and rectal strictures

#### Diagnosis

- Usually clinical. The most specific confirmatory test is the demonstration of high levels of antibody to L1-3 serotypes of *C trachomatis*. The diagnosis may be supported by less specific forms of chlamydia testing—for example, polymerase chain reaction tests on material taken from ulcers or lymph nodes

#### Treatment

- Doxycycline: 100 mg twice a day for 14 days (W), 21 days (E, U, C)
- Azithromycin: 1 g weekly for three weeks
- Erythromycin: 500 mg four times daily for 14 days (W), 21 days (E, U, C)

C= Centers for Disease Control, USA; E=European STI guidelines; U=UK National Guidelines; W= World Health Organization

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### Multiple painless ulcers

Secondary syphilis can result in multiple eroded papules or mucous patches.

Trauma as a result of sex or other causes can cause multiple or solitary erosions or ulcers.



Primary syphilis

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### Donovanosis (Granuloma inguinale)

#### Cause

- *Klebsiella* (formerly *Calymmatobacterium*) *granulomatis*

#### Distribution

- Localised areas of India, Brazil, South Africa, Papua New Guinea

#### Incubation period

- Two to 40 days

#### Main symptoms

- Slow-growing, painless, friable genital and inguinal lesions that often stand out from the skin

#### Complication

- Genital lymphoedema, pelvic lesions in women, rarely haematogenous dissemination to bone and other viscera

#### Diagnosis

- Demonstration of intracellular bacteria (Donovan bodies) in material taken from lesions

#### Treatment

All treatments given until cured or at least two weeks (E) or three weeks (C):

- Azithromycin: 500 mg daily (C, E, U, W) or 1g weekly (C, E, U)
- Doxycycline: 100 mg twice daily (C, E, U, W)
- Erythromycin: 500 mg four times daily (C, E, U, W)
- Ceftriaxone: 1 g intramuscularly daily
- Ciprofloxacin: 750 mg daily (C)

C=Centers for Disease Control, USA; E=European STI guidelines; U=UK National Guidelines; W= World Health Organization

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## Diagnosis of genital ulcers

- Although some people who present with genital ulceration have the classic signs and symptoms described above, many individuals present atypically
- Basing the diagnosis on appearance alone has been shown to be suboptimal
- Where laboratory facilities exist, every attempt should be made to confirm the diagnosis either microbiologically or histologically, as appropriate
- In the absence of laboratory facilities, syndromic management should be used to cover treatment for the most probable infectious causes, with onward referral if the ulceration fails to respond to first and second line therapy

## Genital herpes

Genital herpes is a common infection caused by the herpes simplex virus (HSV). HSV has two viral subtypes: type 1 (HSV-1) and type 2 (HSV-2). Classically, genital herpes is caused by infection with HSV-2. In recent years, however, childhood infection with HSV-1, the cause of orolabial herpes (cold sores), has become less common, at least in western countries. This means that an increasing number of people are becoming sexually active when they are uninfected with HSV-1 and hence are susceptible to infection.

Genital HSV-1 acquired through orogenital contact is the most common cause of first episode genital herpes in the United Kingdom, particularly in young people. Genital infection with HSV-1 is clinically indistinguishable from HSV-2.

### Natural course

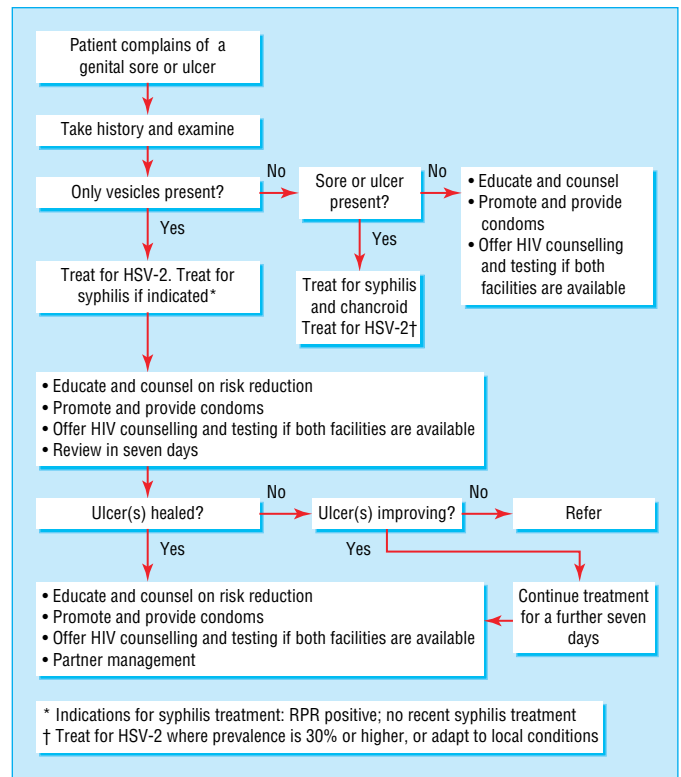
The incubation period for HSV is one to two weeks; however, only about half of the people that get infected have symptoms of genital herpes at the time of their infection with either HSV-1 or HSV-2. Some people will become symptomatic at later date and others will remain asymptomatic. Therefore, the reported cases of symptomatic disease greatly underestimate the total burden of infection. Infected individuals who are totally asymptomatic and unaware of their infection can transmit the infection to their partners.

Seroepidemiological studies from the United States indicate that 22% of the adult population are infected with HSV-2. The rates in Europe are lower, with rates in the United Kingdom around 7%. Studies from developing countries indicate very high rates of infection, for example over 40% of Tanzanian women have become infected by age 19 years.

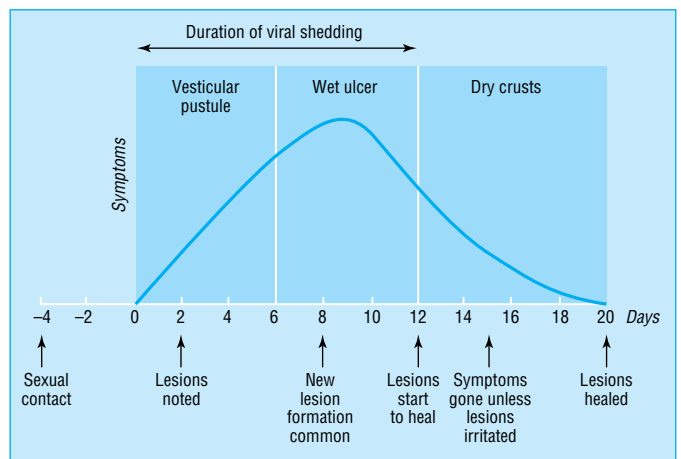
Genital herpes is a lifelong chronic condition. After infection, the virus becomes latent in the local sensory ganglion, periodically reactivating to cause symptoms, such as genital ulceration (a recurrence) or asymptomatic, but nonetheless infectious, viral shedding.

Genital HSV-2 recurs and is shed more often than genital HSV-1 (the converse is true for oral infection). On average, people with symptomatic genital HSV-2 get a symptomatic recurrence around four times per year (although the range is wide—from none to more than twelve recurrences per year). Asymptomatic shedding may be more frequent than this. As a general rule, the frequency of recurrences and shedding reduces over time.

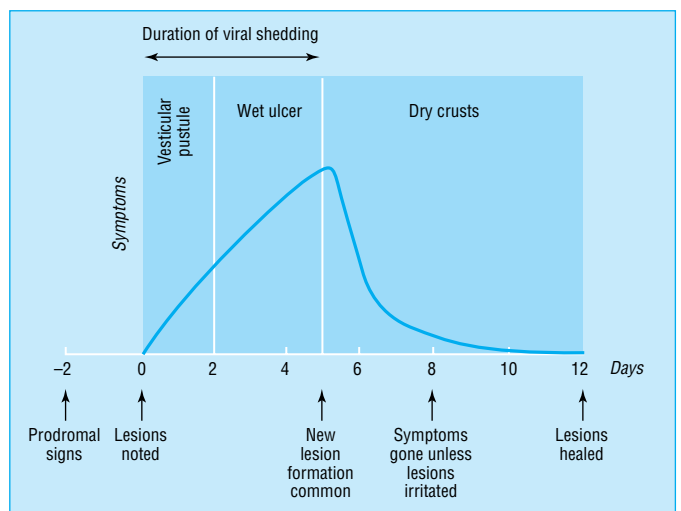
People with symptomatic genital HSV-1 typically have around one recurrence per year (again the range is wide). Although symptoms usually occur at the site where HSV enters the body, such as the genital area, recurrences may occur anywhere in the distribution of that dermatome, typically on the buttocks or thighs.



Genital ulcer disease flow chart



Course of first episode genital herpes



Course of recurrent genital herpes

**Clinical presentation: first episode infection**

The first time a person has clinical symptoms of genital herpes is called the “first episode.” It usually presents with multiple painful genital ulcers. Typical lesions start as vesicles, which then become superficial ulcers that crust and heal. Separate lesions may coalesce to form substantial areas of superficial ulceration. Viral shedding lasts until lesions have crusted over.

More recently, it has been recognised that atypical presentations are common. Small erosions or fissures may be caused by HSV, as can dysuria in the absence of any obvious lesions. One third of patients may have constitutional symptoms including fever and malaise. About 10% of patients have a headache and photophobia, and symptoms of viral meningitis can occur. A few people complain of retention of urine, either because it is too painful to pass urine over the lesions (urinating in a bath of warm water, which dilutes the urine as it passes over the ulcers, may help) or because of temporary viral autonomic neuritis.

**Clinical presentation: recurrent episodes**

Recurrent episodes are generally less severe and are not caused by reinfection. It is common not to have an identifiable trigger, although trauma (for example due to sexual intercourse) and ultraviolet light can both precipitate infections. Recurrences generally occur more often in the first year of infection, and genital HSV-2 infection is more likely to become recurrent than genital HSV-1. Some people notice prodromal symptoms before a recurrence, typically tingling in the distribution of the sciatic nerve. However, prodromal symptoms are not always followed by a clinical recurrence. Infectious viral shedding can occur during prodromal symptoms.

**Diagnosis**

Genital herpes is diagnosed by isolating the virus directly from genital lesions by culture, polymerase chain reaction, or antigen detection. Other causes of genital ulceration may need to be excluded. Infection can also be confirmed by detecting antibodies to HSV-1 or HSV-2 in a blood sample using type specific antibody tests. Although these antibody tests can be used to confirm or refute infection, they do not give information about the site of infection or whether the individual is symptomatic. In people with their first symptoms of genital herpes it can be determined whether it was acquired recently by taking serial blood samples. The first blood sample is taken at the time of presentation (which will be negative if herpes is recently acquired) and the second sample is taken three weeks later (by which time it should be positive).

**Treatment: first episode**

Patients who present within five days of the start of the episode or while new lesions are still forming should be given oral antiviral drugs, such as aciclovir, famciclovir, or valaciclovir, which are all highly effective in reducing the severity and duration of the episode. They should be started as soon as possible after the start of symptoms. Even if the symptoms and signs of the first episode seem to be minor, treatment should be started, as this may prevent much more severe symptoms developing. Supportive therapy, such as analgesics, should also be considered.

Lay perceptions of herpes are that it is a severe and stigmatising condition. Because infection can only be managed, not eradicated, many people need time and support to come to terms with the diagnosis.



First episode genital herpes

**Clinical presentation of first episode genital herpes**

Site	Symptoms					
	Pain	Dysuria	Retention	Constipation	Discharge	None
Penis (glans, coronal sulcus and shaft)	+					±
Urethra (male)	++	+	+		+	+
Anus/rectum	+		±	+	+	+
Buttocks/thighs/scrotum	+					
Vulva/urethra	++	+	±		±	±
Vagina	+				+	±
Cervix	+				++	+

**Counselling**

When counselling patients with first episode genital herpes, the following issues should be discussed

- Possible source of infection
- Natural course, including risk of subclinical viral shedding
- Future treatment options
- Risk of transmission by sexual and other means
- Risks of transmission to the fetus during pregnancy and the advisability of the obstetrician or midwife being informed
- Sequelae of infected men infecting their uninfected partners during pregnancy
- The possibility of partner notification

**A minority of people have persistent psychological distress and need ongoing psychological support. Providing correct information and support may prevent the development of more severe psychological sequelae**

**Couples in which only one of the partnership is infected with genital herpes need to decide how important it is to prevent transmission and, therefore, to use condoms on a long term basis. Some uninfected partners will prefer to “risk” acquiring HSV rather than use condoms indefinitely, whereas others will continue to use condoms for the foreseeable future**



# ABC of Sexually Transmitted Infections

## Treatment: recurrent infection

Genital herpes recurrences are self limiting and generally cause minor symptoms. Decisions about how best to manage clinical recurrences should be made with the patient. Treatment may be supportive therapy only, episodic antiviral treatments, and suppressive antiviral therapy. The most appropriate strategy for managing an individual patient may vary over time, according to recurrence frequency, symptom severity, and relationship status.

Supportive treatment includes saline bathing and application of petrolatum. Oral aciclovir, valaciclovir, and famciclovir given at the time of the episode are effective at reducing the duration and severity of a recurrence (the median reduction in duration is one to two days for most patients). If given early in the episode, treatment may abort the recurrence. For patients with frequent recurrences, continuous daily antiviral drugs greatly reduce the frequency of recurrences.

## Transmission

Herpes simplex is transmitted when the infectious virus comes in contact with mucous membranes or abraded skin. The infectious virus can be shed during a period of clinical symptoms, prodromal symptoms, or in the absence of symptoms. Therefore, people infected with genital herpes should be advised to abstain from sex during clinical recurrences or when they have prodromal symptoms. However, people should be aware that they may be infectious to their sexual partners between recurrences. The frequency of asymptomatic shedding, is linked closely to the frequency of clinical shedding, so that people with frequently recurring symptoms will probably shed virus often between clinical recurrences.

Infection is much more easily transmitted from men to women than from women to men. However, recent research showed that male condom use can reduce the risk of male to female transmission substantially. As female to male transmission occurs much less often, it has been more difficult to show whether condoms are effective in preventing transmission.

Antiviral drugs such as aciclovir, valaciclovir, or famciclovir dramatically reduce levels of asymptomatic genital shedding of virus. Trials are underway to see if this results in a reduced transmission risk. One large study of once daily valaciclovir has confirmed that this reduction results in a reduced risk of transmission between sexual partners.

## Partner notification

Partners of people with first episode genital herpes may benefit from partner notification because they may have unrecognised genital herpes that can be appropriately diagnosed and managed.

The line drawings showing the courses of first episode and recurrent genital herpes are with permission of Dr L Corey

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## Overview of genital herpes

### Cause

- HSV-1 and HSV-2

### Site of infection

- Site of exposure
- HSV-1 acquired through orogenital contact
- HSV-2 through genital contact

### Incubation period

- One to two weeks
- Asymptomatic infection can occur
- Genital herpes is a lifelong chronic condition
- The virus becomes latent in a local sensory ganglion

### Main symptoms

#### First episode

- Multiple painful genital ulcers starting as vesicles
- Constitutional symptoms, for example fever, malaise, headache, photophobia, and occasional retention of urine

#### Recurrent episodes

- Less severe ulceration, sometimes preceded by prodromal symptoms, for example tingling

### Diagnosis

- Isolate virus from genital lesions by culture, polymerase chain reaction, or antigen detection

### Treatment of first episode (all for five days)

- Aciclovir (200 mg five times daily)
- Famciclovir (250 mg three times daily)
- Valaciclovir (500 mg twice daily)

### Episodic treatment (all for five days)

- Aciclovir (200 mg four times daily)
- Valaciclovir (500 mg twice daily)
- Famciclovir (125 mg twice daily)

### Suppressive therapy

- Aciclovir (400 mg twice daily)
  - Valaciclovir (250 mg twice daily or 500 mg once daily)
  - Famciclovir (250 mg twice daily)
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## Further reading

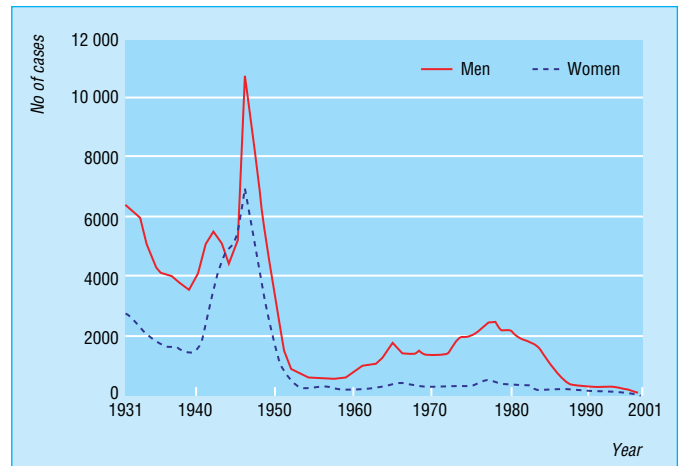
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# 12 Syphilis—clinical features, diagnosis, and management

Michael Adler, Patrick French

The advent of penicillin had a dramatic and rapid impact on the incidence of early infectious syphilis throughout the world in the late 1940s. In England and Wales, the number of cases of syphilis seen in the sexually transmitted infection (STI) clinics has declined substantially since the peak after the second world war. More recently, since 1998, the rate of infectious syphilis has increased substantially. Outbreaks have occurred in Brighton, Manchester, and London, mostly as a result of homosexual transmission. Between 1996 and 2002, new diagnoses have increased tenfold (122 to 1193 cases).

Elsewhere in the world, syphilis still presents a major clinical problem and the World Health Organization estimates that 12 million new cases of infectious syphilis are diagnosed worldwide each year. Most of these cases occur in South and South East Asia (4 million) and sub-Saharan Africa (4 million). In other countries, such as the United States and Russia, syphilis is still a major problem. In the United States, infectious syphilis increased substantially during the 1990s, particularly affecting the African-American community. The numbers of cases are now declining but are still high. Infectious syphilis has reached epidemic proportions in Eastern Europe, particularly the newly independent states of the former Soviet Union.



New cases of infectious syphilis seen in genitourinary medicine clinics in England and Wales, 1931-2001. Adapted from the PHLS Communicable Diseases Surveillance Centre. *Communicable Disease Report* 1997;7:22

Acquired syphilis has been classified traditionally as either early infectious or late non-infectious. The arbitrary cut off point between these stages is usually two years

## Time after exposure

### Early infectious

Primary	9-90 days
Secondary	Six weeks to six months (Four to eight weeks after primary lesion)

Latent (early) <Two years

### Late (non-infectious)

Latent (late)	>Two years
Neurosyphilis	3-20 years
Cardiovascular syphilis	>10-40 years
Gummatous syphilis	3-12 years after primary infection

## Sites of primary syphilis

### Genital

- Shaft of penis
- Coronal sulcus
- Glans penis
- Prepuce
- Fraenum
- Urethral meatus
- Anal margin and canal
- Rectum
- Labia minora, labia majora
- Fourchette
- Clitoris

- Vaginal wall
- Cervix

### Extragenital

- Lip
- Tongue
- Mouth, tonsil, pharynx
- Fingers
- Eyelid
- Nipple
- Any part of the skin or mucous membranes

## Primary syphilis

The incubation period for primary syphilis is 9-90 days (mean 21 days). Lesions are found at the site of inoculation, which may sometimes be extragenital.

The lesion is normally solitary and painless. It first develops as a red macule that progresses to a papule and finally ulcerates. This ulcer is usually round and clean with an indurated base and edges. Inguinal lymph nodes are moderately enlarged, rubbery, painless, and discrete.

The primary lesions will heal within 3-10 weeks and may go unnoticed by the patient. Lesions on the cervix, rectum, and anal canal and margin may, in particular, be asymptomatic.



Primary chancre of vulva



Primary chancre of penis

## Secondary syphilis

The lesions of secondary syphilis usually occur four to eight weeks after appearance of the primary lesion. In about one third of cases the primary lesion is still present. The lesions are generalised, affecting both skin and mucous membranes.

The skin lesions are usually symmetrical and non-itchy. They can be macular, papular, papulosquamous, and, very rarely, pustular. The macular lesions (0.5-1 cm in diameter) appear on the shoulders, chest, back, abdomen, and arms. The papular lesions are coppery red and are the same size as the macules. They may occur on the trunk, palms, arms, legs, soles, face, and genitalia. Skin lesions are commonly a mixture of macular and papular lesions (maculopapular).

In warm, opposed areas of the body, such as the anus and labia, papular lesions can become large and coalesce to form large, fleshy masses (condylomata lata). The papulosquamous lesions are found when scaling of the papules occurs and can be seen in association with straightforward papular lesions. If papulosquamous lesions occur on the palms or soles they are sometimes described as psoriasiform.

Pustular lesions are rare and occur when the papular lesions undergo central necrosis. Mucous membrane lesions are shallow, painless erosions that are usually found in association with papular skin lesions and affect the mucous surface of the lips, cheeks, tongue, face, pharynx, larynx, nose, vulva, vagina, glans penis, prepuce, and cervix. They have a greyish appearance and are sometimes described as "snail track" ulcers.

The lesions of the skin and mucous membrane may be associated with non-specific constitutional symptoms of malaise, fever, anorexia, and generalised lymphadenopathy. The secondary stage is one of bacteraemia, and any organ may show evidence of this, for example hepatitis, iritis, meningitis, and optic neuritis with papilloedema.

Without treatment, the symptoms and signs of secondary syphilis resolve. About one quarter of untreated patients have recurrent episodes of secondary syphilis. Recurrent secondary syphilis is rare after the first year of infection.

## Syphilis in HIV positive patients

Syphilis enhances HIV acquisition and transmission. Although most HIV positive patients with syphilis present with typical features, the classical clinical features described previously can be modified and altered. Features of syphilis can be mistaken for clinical signs of HIV infection.

### Clinical manifestations shared by syphilis and HIV

- Generalised lymphadenopathy
- Skin rashes or alopecia or both
- Oral manifestations (mouth ulcerations)
- Cognitive impairment
- Meningitis
- Cranial nerve palsies
- Myelopathies
- Uveitis

## Latent syphilis

People with untreated syphilis but no signs or symptoms of infection have latent syphilis. This latent period is divided into an early stage, in which the disease has been present for less

### Clinical features of secondary syphilis

Skin lesions	75-80%
Mucous membrane lesions	30%
Generalised lymphadenopathy	50-60%
Arthritis, arthralgia, and periostitis	
Hepatitis	} Rare (<10%)
Glomerulonephritis and nephritic syndrome	
Iridocyclitis and choroidoretinitis	
Neurological disease (meningitis and cranial nerve palsies)	
Alopecia	

### Lesions of secondary syphilis

Skin	Macular or papular Condylomata lata Papulosquamous Pustular
Mucous membranes	Erosions



Maculopapular rash on hands



Maculopapular rash on chest (left) and condylomata lata (right)

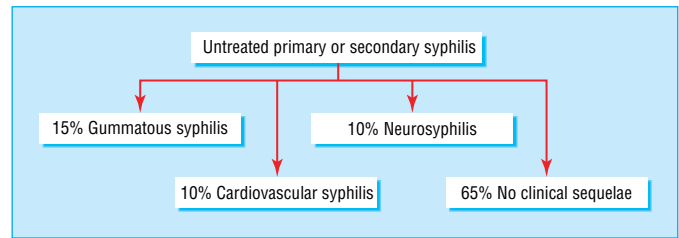
### Syphilis in HIV positive patients

- Increased risk of multiple and larger ulcers in primary syphilis
- Increased risk of genital ulceration in secondary syphilis
- Possibly accelerated development of neurosyphilis, uveitis, and gummata

than two years, and a late stage, in which the disease has been present for more than two years. The condition is diagnosed by

- Positive results from serological tests
- No clinical evidence of early or late syphilis in any system
- Normal results on chest radiography and screening
- Examination of cerebrospinal fluid to exclude cardiovascular syphilis or neurosyphilis.

About 65% of patients with untreated syphilis will not develop late clinical sequelae of the disease. However, about 10% of patients will develop neurological lesions, 10% will develop cardiovascular lesions, and 15% will develop gummatous lesions. It is extremely rare to see late syphilis in the developed world because of the decline in infectious syphilis and improved clinics and treatment facilities.



Course of untreated syphilis

## Neurosyphilis

Neurosyphilis is classified as asymptomatic, meningovascular, and parenchymatous (general paralysis of the insane and tabes dorsalis). The widespread use of antibiotics for other unrelated conditions has probably resulted in neurosyphilis that does not always fit the older classical clinical forms and descriptions.

### Meningovascular syphilis

This can be present in the early and late stages of syphilis. Patients can present with acute meningeal involvement during the secondary stages of the disease, which often coincides with the development of skin lesions. Headache is the main symptom.

Signs of meningitis are found with third, sixth, and eighth cranial nerve involvement, papilloedema, and, rarely, homonymous hemianopia or hemiplegia. Late meningovascular syphilis presents less acutely but headaches may still be a presenting symptom. Cranial nerve palsies (third, sixth, seventh, and eighth) and pupillary abnormalities are seen. The pupils are small and unequal in size and react to accommodation but not light (Argyll Robertson pupils). Cerebral and spinal cord (anterior spinal artery) vessels may be affected.

### Parenchymatous neurosyphilis

This may present as general paralysis of the insane or tabes dorsalis, or, rarely, as a combination of the two. General paralysis with resulting cerebral atrophy occurs 10-20 years after the original primary infection.

Tabes dorsalis is characterised by increasing ataxia, failing vision, sphincter disturbances, and attacks of severe pain. These pains are described as “lightning” because they occur as acute stabbing pain mostly in the legs. The signs of tabes dorsalis are largely caused by degeneration of the posterior columns: absent ankle and knee reflexes (rarely biceps and triceps), impaired vibration and position sense, and a positive Romberg’s sign.

### Asymptomatic neurosyphilis

As the name implies, no neurological symptoms or signs are detected in asymptomatic neurosyphilis and the diagnosis is based entirely on changes in the cerebrospinal fluid and serum.

## Cardiovascular syphilis

This most commonly occurs in large vessels, particularly the aorta, but medium and small sized vessels may also be affected. The aorta is affected by an aortitis (with or without coronary ostial stenosis), aneurysm of the ascending part, and aortic incompetence. The symptoms of an aneurysm affecting the arch usually result from the pressure on structures within the

**Epilepsy, confusion, aphasia, monoplegia, hemiplegia, or paraplegia are just some of the ways in which late meningovascular syphilis can present**

### General paralysis of the insane

#### Early

- Irritability
- Fatigability
- Inefficiency
- Personality changes
- Headaches
- Impaired memory
- Tremors

#### Late

- Defective judgment
- Lack of insight
- Depression or euphoria
- Confusion and disorientation
- Delusions
- Seizures
- Transient paralysis and aphasia

#### Signs

- Expressionless facies
- Tremor of lips, tongue, and hands
- Dysarthria
- Impairment of handwriting
- Hyperactive tendon reflexes
- Pupillary abnormalities
- Optic atrophy
- Convulsions
- Extensor plantar responses

### Tabes dorsalis

#### Symptoms

- Lightning pains
- Ataxia
- Bladder disturbance
- Paraesthesiae
- Tabetic crises
- Visual loss
- Rectal incontinence
- Deafness
- Impotence

#### Signs

- Argyll Robertson pupils
- Absent ankle reflexes
- Absent knee reflexes
- Absent biceps and triceps reflexes
- Romberg’s sign
- Impaired vibration sense
- Impaired position sense
- Impaired sense of touch and pain
- Optic atrophy
- Ocular palsies
- Charcot’s joints

## ABC of Sexually Transmitted Infections

superior mediastinum. Thus, stridor and cough (trachea), dysphagia (oesophagus), breathlessness (left bronchus), hoarseness (left recurrent laryngeal nerve), and Horner's syndrome (sympathetic chain) may occur. Finally, pressure on the superior vena cava can result in congested veins in the head and neck as well as cyanosis. The signs of cardiovascular disease are no different from those of aortic incompetence and aneurysms from other causes.

### Gummas

These are granulomatous lesions that develop 3-12 years after the primary infection. Gummas may occur on the skin or mucous membranes and in bone or viscera. Skin lesions are usually nodular. They can occur anywhere on the skin and are found as small groups of painless lesions that are indolent, firm, coppery red, and about 0.5-1 cm in diameter.

If subcutaneous tissue is affected, the lesions start as smooth, hard swellings that eventually break down to well circumscribed, punched out ulcers, which, when they heal, leave typical tissue paper scarring. These often occur on the leg, face, and scalp. Lesions in mucous membrane are punched out ulcers on the hard and soft palate, uvula, tongue, larynx, pharynx, and nasal septum. Bone and visceral gummas are extremely rare, but affect the tibia, skull, clavicle, sternum, femur, liver, brain, oesophagus, stomach, lung, and testes.

### Diagnosis and management

Establishing a diagnosis of syphilis can sometimes be difficult, and it is reasonable for all suspected cases to be referred to or discussed with an STI specialist. The diagnosis can be confirmed by history, physical examination, and one or all of dark ground microscopy, serology, examination of cerebrospinal fluid, and radiology. The application and interpretation of these investigations depend on the clinical stage of the syphilis.

#### History and examination

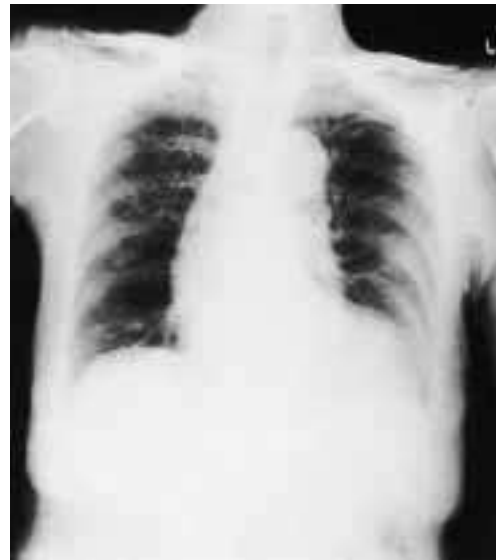
Assessment of an individual suspected to have syphilis should (in addition to the assessment outlined in Chapters 3 and 4) include a careful history of previous syphilis screening and previous diagnosis of syphilis. If a diagnosis of syphilis has been made in the past, then it is important to attempt to determine the stage of disease, the treatment given, and the serological response to treatment, particularly the venereal disease research laboratory (VDRL) or the rapid plasmin reagin (RPR) titre (see below). History taking should also inquire about possible symptoms of early and late syphilis.

#### Dark ground microscopy

This test can be used to establish the diagnosis from the lesions of primary and secondary syphilis or occasionally from material obtained by puncture of the inguinal nodes (especially if a topical antiseptic or antibiotic has been applied or if lesions are healed or concealed). The presence of oral commensal treponemes makes microscopy unreliable for mouth lesions.

Three separate specimens from the lesion(s) should be examined by dark ground microscopy initially and, if necessary, on three consecutive days. This is done by cleaning the lesion with a gauze swab soaked in normal saline and squeezing it to encourage a serum exudate. The serum is then scraped off the lesion and placed on the three slides.

Dark ground microscopy is a vital test in primary syphilis because it may be the only means of establishing a positive diagnosis. Considerable experience is required to recognise



Cardiovascular syphilis—aneurysm of the ascending aorta and cardiomegaly



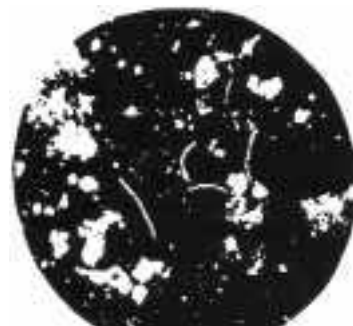
Gummas on the lower limb

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#### Diagnostic criteria for syphilis

- History
  - Physical examination
  - Dark ground microscopy
  - Serology
  - Lumbar puncture
  - Chest radiography and screening
- 

**An examination should focus on determining whether the patient has any signs of early syphilis or the manifestations of late complications, particularly neurological and cardiovascular disease**



Dark ground microscopy of *Treponema pallidum*

*Treponema pallidum*. It is bluish white, closely coiled (8-24 coils), and 6-20 µm long. The treponeme has three characteristic movements: watch spring, corkscrew, and angular.

**Serological tests**

The serological tests used to diagnose syphilis are either non-specific (non-treponemal) or specific (treponemal). Specific tests for syphilis are useful for confirming the diagnosis particularly at first presentation; however, these tests usually remain positive throughout a patient’s life, even after successful treatment. Non-specific tests are useful to monitor the response to treatment and for diagnosing reinfection of syphilis. However, they may also give false positive tests in a variety of conditions.

The most widely used non-specific tests are either the VDRL test or the RPR test. These tests depend on the appearance of antibody (reagin) in the serum, and this usually occurs between three and five weeks after the patient has contracted the infection. They are both quantitative tests and this can be useful in assessing the stage and activity of the disease. Decreasing titres are associated with treatment response and increasing titres are associated with treatment failure and reinfection. However, VDRL and RPR titres also decay naturally without treatment, so untreated patients may have active disease despite low titre or negative RPR and VDRL results.

Both tests may yield biological false positive reactions to acute infections (such as herpes viruses, measles, and mumps) or after immunisation against typhoid or yellow fever. Chronic causes of biological false positive reactions include autoimmune diseases and rheumatoid arthritis.

**Specific tests**

The specific tests include the more recently available *T pallidum* enzyme immunoassay (EIA) tests that are beginning to replace the fluorescent treponemal antibody test (FTA) and *T pallidum* haemagglutination assay (TPHA) test as the specific tests of syphilis screening. The EIA tests have the advantage of becoming positive early on in the course of infection and are easier to automate. The FTA and EIA tests are usually the first to become positive—between three and four weeks after infection. These tests are positive in 85-90% of cases of primary syphilis. In early syphilis these may be the only positive serological tests.

Specific and non-specific tests are also positive in other treponemal conditions that are similar to syphilis, such as yaws, bejel, and pinta. Bejel and pinta are unusual conditions; however, yaws remains endemic in a number of countries around the world. Yaws is caused by the spirochaete *T pertenuae*. It is usually an infection acquired in childhood and is characterised by skin ulceration, usually of the lower limbs.

Abnormalities of the cerebrospinal fluid may be found at any stage of syphilis and are common in early syphilis (particularly the secondary stage). Lumbar puncture is not routinely required in early syphilis or in asymptomatic late syphilis; however, it is important that all patients with suspected neurosyphilis have a full neurological examination and cerebrospinal fluid (CSF) assessment. Some specialists also recommend that all patients with HIV infection and syphilis for more than two years should have a lumbar puncture to assess possible neurological involvement (see below).

Most patients with neurosyphilis will have a cell count above 5×10<sup>6</sup> lymphocytes/l and a protein level above 40 g/l. Provided that the CSF is not contaminated with macroscopic blood, the treponemal and non-treponemal tests are useful to diagnose neurosyphilis. Most patients with positive CSF RPR, or VDRL tests will have neurosyphilis, although people with probable neurosyphilis have negative non-specific tests. Although many

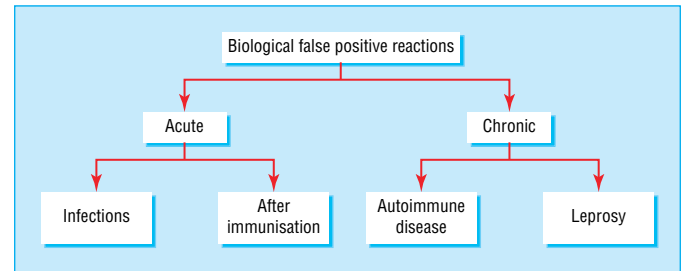
**Serological tests**

Non-specific

- Venereal Disease Reference Laboratory (VDRL)
- Rapid Plasmin Reagin (RPR)

Specific

- *T pallidum* EIA test
- Absorbed fluorescent treponemal antibody (FTA) test
- *T pallidum* haemagglutination (TPHA) test



Biological false positive reactions to serological tests

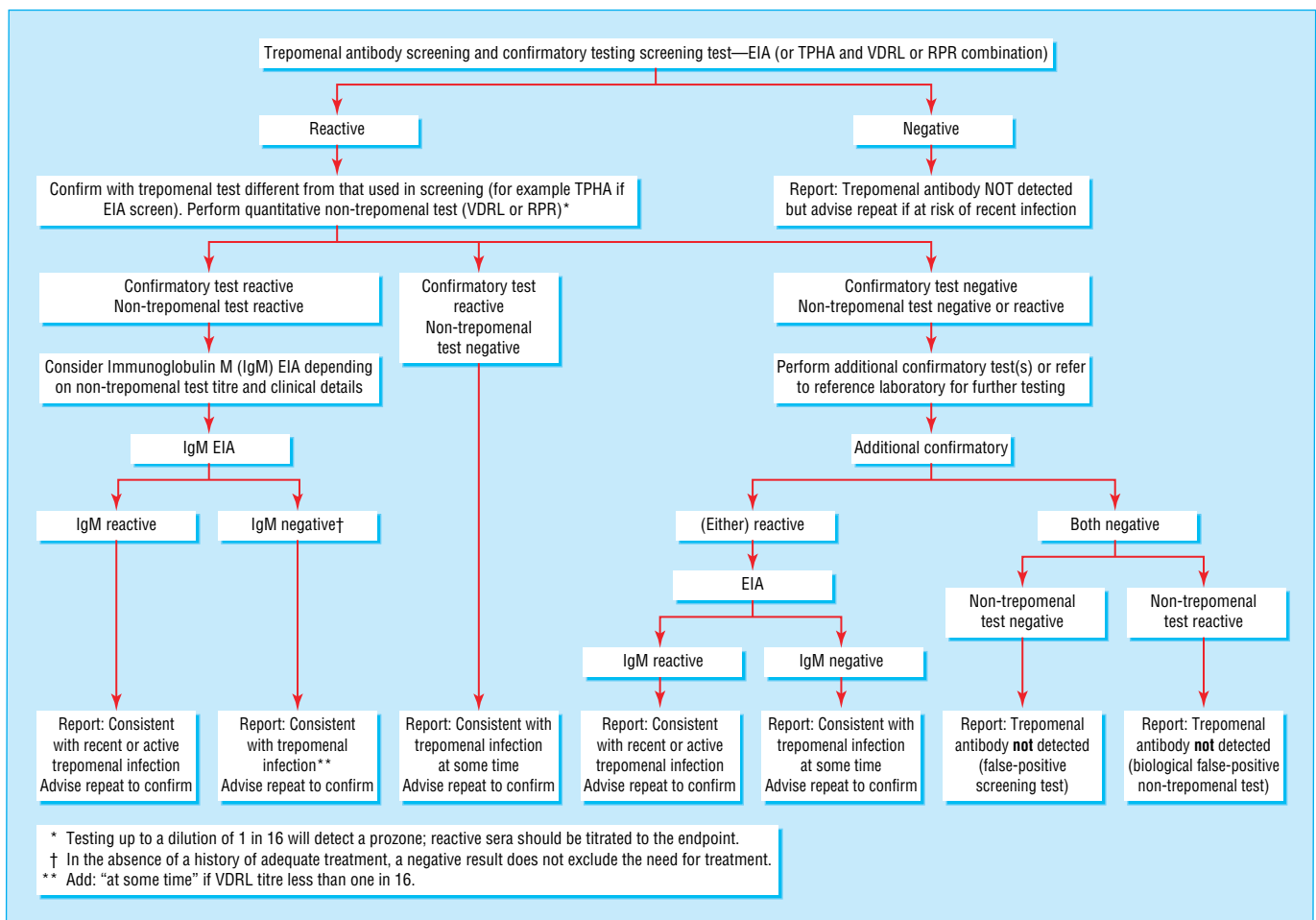
**It is possible that all serological tests may be negative in early primary infection. The TPHA test is the last of the commonly used tests to become positive (between four and eight weeks after infection). The positive syphilis serology can only be interpreted in the light of the history and clinical findings so is important to use a systematic approach to both the screening and subsequent confirmatory tests before making a diagnosis**

**Diagnosis and serological interpretation**

Results positive	Diagnosis
None	Syphilis not present or very early primary syphilis
All	Untreated, recently treated, or latent syphilis
<i>T pallidum</i> EIA (or FTA) and VDRL	Primary syphilis
<i>T pallidum</i> EIA (or FTA) and TPHA	Treated syphilis or untreated late latent or late syphilis
<i>T pallidum</i> EIA or FTA only	Early primary syphilis—untreated or recently treated early syphilis
VDRL/RPR only	False positive reaction

**Cerebrospinal fluid and radiology**

- CSF investigations
- Cell count
- Total protein
- VDRL or RPR, TPHA, and FTA
- Radiology
- Chest x ray (posteroanterior and lateral)



Syphilis (treponemal) screening and interpretation algorithm, Public Health Laboratory Service, United Kingdom, 2000

individuals have positive FTA or TPHA in the CSF, negative tests virtually rule out neurosyphilis.

The final diagnostic procedure in the assessment of a patient with latent syphilis or suspected cardiovascular disease is chest radiography (posterior and anterior and left lateral) to show the arch of the aorta and to screen for aortic dilatation. If the examination and investigations show aortic involvement then more specialised tests and referral to cardiologists are usually indicated.

## Treatment and prognosis

Penicillin remains the cornerstone of treatment for all types of syphilis. In primary and secondary syphilis, treatment can be either given in a form of benzathine penicillin as a single injection or 10 days of procaine penicillin. Patients with penicillin allergy or patients who decline parenteral treatment can be prescribed doxycycline therapy.

Some specialists recommend that steroids should be used at the start of treatment for late syphilis because of a potential risk that focal oedema and swelling may lead to cerebral or coronary artery occlusion.

The prognosis of treated syphilis depends on the stage of the disease and the degree of tissue damage in cardiovascular and neurological syphilis. Adequate treatment of primary, secondary and latent syphilis will always halt the progression of the disease. The prognosis in symptomatic neurosyphilis is variable. Although, in general, the inflammatory process is arrested by adequate treatment, tissue damage may be too great to prevent an improvement in symptoms. In cardiovascular disease, the

**The Jarisch-Herxheimer reaction is common in primary and secondary syphilis and patients must be warned that fever and flu like symptoms may occur 3-12 h after the first injection; occasionally the chancre or skin lesions enlarge or become more widespread. Reassurance and antipyretics, such as paracetamol and non-steroid anti-inflammatory agents, are usually all that is required**

onset of symptoms usually indicates established aortic medial necrosis that is not reversed by treatment.

For a patient with early infectious syphilis, contact tracing must be carried out on all sexual contacts in the previous three to six months. In late syphilis when a patient is no longer infectious, serological testing is probably only practicable in the patient's regular partner(s). If late syphilis is diagnosed in a mother it may be necessary to test her children (see Chapter 9).

### HIV infection and syphilis

Although more rapid progression to late stage syphilis has been reported when associated with HIV infection, most HIV positive individuals who have syphilis present with symptoms and signs identical to those individuals who are HIV negative. However, all patients who have syphilis should be offered HIV testing and all HIV positive individuals should be screened for syphilis.

**Serological tests in HIV positive patients are usually reliable in syphilis and most specialists treat patients with syphilis with the same regimens that are recommended for individuals who are HIV negative. However, some specialists remain concerned that early neurological involvement of syphilis in HIV positive individuals is a considerable problem and, therefore, recommend neurological evaluation, lumbar puncture, and syphilis treatment regimens that adequately treat neurosyphilis for all HIV positive individuals with active syphilis**

### Treatment of syphilis

Stage	Standard treatment	Alternatives
Primary and secondary	Benzathine penicillin 2.4 megaunits intramuscularly as a single dose or aqueous procaine penicillin 600 000 units intramuscularly per day for 10 days	Doxycycline 100 mg orally twice a day for 14 days
Latent early (less than two years)	Benzathine penicillin 2.4 megaunits intramuscularly as a single dose or aqueous procaine penicillin 600 000 units per day for 10 days intramuscularly	Doxycycline 100 mg orally twice a day for 14 days
Latent late (more than two years)	Aqueous procaine penicillin 900 000 units intramuscularly per day for 17 days or benzathine penicillin 2.4 megaunits intramuscularly weekly over two weeks (three injections)	Doxycycline 100 mg orally twice a day for 30 days
Neurosyphilis	Aqueous procaine penicillin 2.4 megaunits intramuscularly per day for 17 days (with or without oral prednisolone 20 mg per day starting the day before penicillin treatment and continuing at the same dose for two days after) and oral probenecid 500 mg four times daily	Doxycycline 200 mg orally twice daily for 30 days
Cardiovascular syphilis	Aqueous procaine penicillin 600 000 units intramuscularly per day for 17 days (with or without oral prednisolone 20 mg per day—dosing as above)	Doxycycline 100 mg orally twice daily for 30 days
Gummatous syphilis	Aqueous procaine penicillin 600 000 units intramuscularly per day for 17 days	Doxycycline 100 mg orally twice daily for 30 days

### Overview of syphilis

#### Cause

- *T pallidum*, a spirochaete bacterium

#### Initial site of infection

- Site of exposure, usually genitals, perianal area, or mouth

#### Incubation period

- Usually two to three weeks (range 9-90 days) to primary syphilis

#### Primary syphilis

- Ulceration at site of exposure (incubation as above)

#### Secondary syphilis

- Systemic illness two to three months (range one to six months) after primary syphilis)

#### Early latent syphilis

- Asymptomatic syphilis of less than two years' duration

#### Late latent syphilis

- Asymptomatic syphilis of more than two years' duration

#### Gummata

- Necrotic nodules or plaques—3-12 years after primary infection

#### Neurosyphilis

- "General paralysis of the insane"—10-20 years after primary infection
- Takes dorsalis (dorsal column impairment)—10-20 years after primary infection

#### Meningovascular syphilis

- Early (a part of secondary syphilis)
- Late (2-20 years)

#### Cardiovascular syphilis

- Aortic regurgitation, angina, and aortic aneurysm
- Clinical history and examination 10-40 years after primary infection

#### Diagnosis

- Identification of *T pallidum* in early syphilis
- Serology (specific or non-specific)
- Identification of complications of late syphilis

#### Treatment

- Parenteral penicillin (see text)
- Alternative—doxycycline



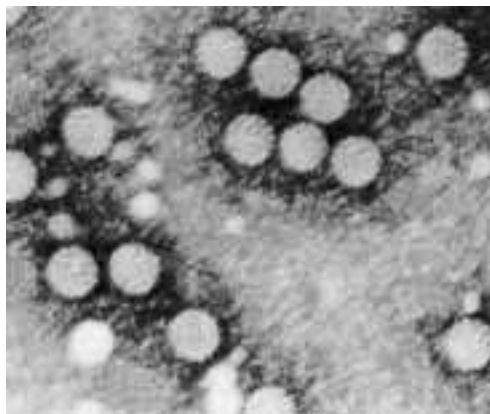
# 13 Genital growths

Michael Adler

## Genital warts

Even though genital warts (condyloma acuminatum) are commonly seen in departments of genitourinary medicine (GUM) (about 131 000 new and recurrent cases a year in the United Kingdom), many more cases are diagnosed and treated by general practitioners, surgeons, gynaecologists, and dermatologists. Not only are warts common, but they also are difficult and time consuming to treat, and certain types are associated with cervical dysplasia.

Genital warts are caused by a small DNA virus, a papillomavirus belonging to the papovavirus group that cannot be cultured. They differ from skin warts histologically and antigenically and are most commonly caused by human papillomavirus (HPV) types 6 or 11 (types 16, 18, 31, 33, and 35 also cause genital warts). Genital warts nearly always are transmitted by sexual contact; autoinoculation from hand to genitals is unusual. Infants and young children may develop laryngeal papillomas as a result of infection from maternal genital warts at delivery. The incubation period is long, varying from two weeks to eight months (mean incubation period is three months).



Papillomavirus

## Clinical features

Genital warts are often asymptomatic and painless. Patients may give a history of suddenly noticing them or noticing them only once their sexual contact has acquired them. Women are more likely to be unaware of warts because it is harder for them to examine their genitalia. Warts flourish in warm, moist conditions, particularly if discharge or other infections are present.

Warts may be solitary but are usually multiple by the time the patient attends for consultation. In men they may be found on the glans and shaft of the penis, prepuce, fraenum and coronal sulcus, urethral meatus, scrotum, anus, and rectum. In women the most common site of infection is the introitus and vulva, but warts may also affect the vagina and (as flat warts) the cervix. Other infected sites are the perineum, anus, and rectum.



Penile warts



Intrameatal wart



Vulval (left) and perianal (right) warts

## Diagnosis

Genital warts are one of the few sexually transmitted conditions that are diagnosed solely from their clinical features. Diagnosis is not usually difficult but the differential diagnosis of condylomata lata of secondary syphilis, molluscum contagiosum, sebaceous cysts, and benign and malignant tumours should be remembered. Warts often may herald other sexually transmitted infections. For example, one third of women who attend GUM departments with genital warts have one or more additional diseases diagnosed concurrently.

All women with genital warts, even in the absence of any other symptoms, must have a full set of microbiological tests to exclude infection with *Candida albicans*, *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and bacterial vaginosis. Heterosexual and homosexual men with penile warts should have urethral tests for gonorrhoea, *C trachomatis* and non-gonococcal urethritis even if they are asymptomatic. Likewise, homosexual men with anal warts should have proctoscopy to exclude the presence of additional warts in the rectum as well as other rectal diseases such as gonorrhoea. Finally, serological tests for syphilis should be carried out in both men and women.

## Complications

Complications of genital warts are rare. Occasionally they may increase alarmingly in size during pregnancy and present as large cauliflower like masses (see Chapter 9). In men, similar giant, benign but destructive warts (Buschke-Löwenstein tumour) may occur on the penis, or existing small ones may rapidly become enlarged. Malignant transformation of vulval, cervical, penile, and anal warts has been reported.

Flat warts on the cervix are not usually apparent to the naked eye. Cervical dysplasia is strongly associated with HPV types 16, 18, 31, 33, and 35, particularly types 16 and 18. Therefore, all women who have had genital warts should have regular cytology by following national guidelines. No changes in screening intervals are required.

## Treatment

Initial treatment is usually with locally applied caustic agents. It is usual to start with podophyllin (a cytotoxic agent), which should be applied to the lesions in strengths of 10% or 15% in industrial spirit and repeated once or even twice a week. As it is an irritating substance it can cause bad burns. Therefore, patients must be told to wash it off between three and four hours after application. Patients may often want to apply podophyllin themselves, but this is undesirable because they may be overzealous in their justifiable desire to get rid of their warts and apply the substance too often, without washing it off, on the basis that "if it hurts it must be doing me good." Severe systemic effects of peripheral neuropathy, coma, and hypokalaemia can occur after application of large quantities.

Podophyllotoxin (0.5%) has less severe side effects and can be used by the patient at home. The patient is told to administer it twice a day for three days and to repeat the application four days later if necessary. Up to four cycles can be administered.

If podophyllin is ineffective after regular application for two or three weeks, the more caustic agent glacial trichloroacetic acid (80-90%) may be used, again with great caution. This agent is more often used for hyperkeratotic warts but, even so, these warts are often resistant and electrocautery or cryotherapy (cryoprobe or cryac spray) will be needed. This can be applied

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### Differential diagnosis of genital warts

- Condylomata lata
  - Molluscum contagiosum
  - Sebaceous cysts
  - Tumours
- 

**Contact tracing and examination of regular sexual partners must be undertaken as well as full microbiological investigations for other sexually transmitted infections. Condom usage is recommended to reduce the level of infection among heterosexual partners**



Massive warts in pregnancy

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### Overview of genital wart infection

#### Cause

- Papillomavirus, particularly types 6 and 11 (also 16, 18, 31, 33, and 35)

#### Site of infection

- Site of exposure—that is the penis, urethral meatus, scrotum, anus, rectum, vulva, vagina, and cervix

#### Complications

- Rare. Increased size during pregnancy, and associated cervical dysplasia (particularly type 16 and 18)

#### Incubation

- Two weeks to 18 months (average three months)

#### Diagnosis

- Clinical features

#### Treatment

- Ablation
-

## ABC of Sexually Transmitted Infections

weekly. Trichloroacetic acid is very corrosive, so it must be applied with care, protecting the surrounding skin with petroleum jelly. Caution or surgical excision should be considered at an earlier stage if the warts are particularly large or numerous.

Other treatments can be used, such as fluorouracil, interferons, and imiquimod. Fluorouracil is a DNA antimetabolite that is made up as a 5% cream. It probably has a limited use because of severe local side effects, such as vulval burning and neovascularisation. It has been used for intrameatal and intravaginal warts in conjunction with laser therapy. Interferons have been used; however, they are expensive, with systemic side effects, and the response rate is not superior to other therapies. Finally, imiquimod, an immune response modifier, can be used as a 5% cream and is most often used for external genital warts by inducing a cytokine response. It is applied to the lesions three times per week and washed off by the patient about 6-10 hours after application. The application can continued for up to 16 weeks as the response to treatment can be delayed for some weeks.



Cryac spray

### Approaches to the treatment of genital warts

Site or type of warts	Start	One week	Two weeks	Three weeks	Four weeks
Few, small, and soft	10-25% podophyllin or podophyllotoxin solution or cryotherapy	→	→	Trichloroacetic acid	Cryotherapy, electrocautery
Solitary, large, and discrete	Electrocautery diathermy, excision, and cryotherapy				
Extensive, multiple vegetations	10-25% podophyllin, podophyllotoxin solution, or trichloroacetic acid	→		→	Cryotherapy, surgical excision
Hyperkeratotic or keratinised	Trichloroacetic acid or cryotherapy	→		Electrocautery, diathermy	
Intrameatal	Cryotherapy	→		Electrocautery, cryotherapy	
Cervical	Colposcopy + biopsy ?→cryotherapy, laser				
Vaginal	Cryotherapy or trichloroacetic acid				
Perianal	Cryotherapy or podophyllotoxin cream				
Pregnancy	None—unless discrete small vaginal, vulval, or introital, then use trichloroacetic acid or cryotherapy—?		Note: do not use podophyllotoxin, podophyllin, fluorouracil, or imiquimod		

During pregnancy it is best to offer no treatment (see Chapter 9). Podophyllin is contraindicated because of its toxicity and possible mutagenic action. Warts usually diminish in size once pregnancy has ended. Trichloroacetic acid may be used if the lesions are discrete, small, and occur on the vaginal wall or vulva. Alternatively, cryotherapy or electrocautery may be offered. In addition, fluorouracil and imiquimod should not be used during pregnancy. Occasionally, caesarean section is necessary if the warts are likely to obstruct labour. Laryngeal and anogenital papilloma can occur in neonates, infants, and children, possibly transmitted transplacentally, perinatally, or postnatally. Whether these are prevented by treating the mother during pregnancy is not known, and it is certainly not an indication on its own for caesarean section.

Doctors who treat genital warts outside GUM departments or sexually transmitted infections clinics should remember, firstly, that an accurate and detailed sexual history is needed;

### Treatment of warts outside GUM departments

- Sexual history
- Exclude a concurrent sexually transmitted infection
- Trace regular sexual contacts

secondly, that concurrent sexually acquired conditions should be excluded; and, thirdly, that contact tracing must be carried out.

## Molluscum contagiosum

Molluscum contagiosum may be transmitted sexually but this is not the only route. It is a contagious viral condition that may be spread by close bodily contact, clothing, or towels. Transmission (outbreaks) is possible in swimming pools, sauna baths, schools, after massage, and between siblings. The agent that causes molluscum contagiosum is one of the pox viruses and has a variable incubation period of 2-12 weeks. Cases are seen in clinics but far more are likely to be seen by general practitioners and dermatologists. The immunocompromised patient with HIV may exhibit lesions, particularly on the face.

The clinical lesions of molluscum contagiosum are characteristic. The pearly white, umbilicated papules are found in the genital area (penis, scrotum, vulva, perineum, abdomen, and thighs), but if transmission is non-sexual they may also be found in any part of the body but particularly on the arms, face, eyelids, and scalp. The lesions are usually small (2–5 mm in diameter).

Diagnosis is usually based on clinical appearance because the virus cannot be grown successfully. Material expressed from the centre of lesions shows viral inclusions in Giemsa stain or on electron microscopy. As the condition may be sexually transmitted, other sexually transmitted infections should be excluded if the patient's history or the site of the lesions (proximity to genital area) indicates that this could be the route of infection.

Treatment is by applying phenol on the end of a sharpened stick to the central umbilicated core of the lesions. This may need to be repeated several times. Alternatively, electrocautery or cryotherapy may be used.



Molluscum contagiosum

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### Further reading

- National Guidelines for the Management of Anogenital Warts [www.agum.org.uk](http://www.agum.org.uk) (accessed 27 Nov 2003)
  - Clinical Effectiveness Group (Association of Genitourinary Medicine and the Medical Society for the Study of Venereal Diseases). National guidelines for the management of anogenital warts and sexually transmitted infections. *Sex Transm Infect* 1999;75:S71-75
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# 14 Genital infestations

Michael Adler

## Pediculosis pubis

This infestation is caused by the pubic louse, *Phthirus pubis*, which is a different species from the one that causes head and body louse infestation (pediculosis capitis and pediculosis corporis). The insect is small and round (1-2mm long) and has three sets of legs. The adult is a blood sucker and adheres not only to pubic hair but also to other hairy areas (perineum, thighs, abdomen, axillas, eyebrows, and eyelashes). The female lays eggs (nits) at the base of the hairs and these usually hatch within seven days. The adult louse is transferred from person to person during close bodily contact. As lice do not leave the host, the infestation is not spread by wearing infested clothing or sleeping in infested sheets. The patient may complain of irritation. Sometimes the condition is asymptomatic and the patient may be horrified to find the adult louse or nits on their body.

Diagnosis is usually based on clinical appearances alone. A hand lens is useful during the examination and a suspected louse or eggs (nits) on a hair may be removed and viewed under a low power microscope. Bluish grey macules occasionally occur on the abdomen, buttocks, or thighs at the site of the bites. As the condition is usually acquired sexually, a full sexual history should be taken and the patient examined for other sexually transmitted infections.

Pediculosis pubis is treated by applying malathion (0.5%), permethrin (1% cream rinse), phenothrin (0.2%), or carbaryl (0.5-1%) to all hairy areas except the scalp but including the beard and moustache. The patient should not wash this off for 24 hours, after which a bath should be taken. Usually one application is enough, but a heavy infestation will necessitate further treatment within 7-10 days. Sexual partners should also be seen and treated. Shaving body hair is not necessary.

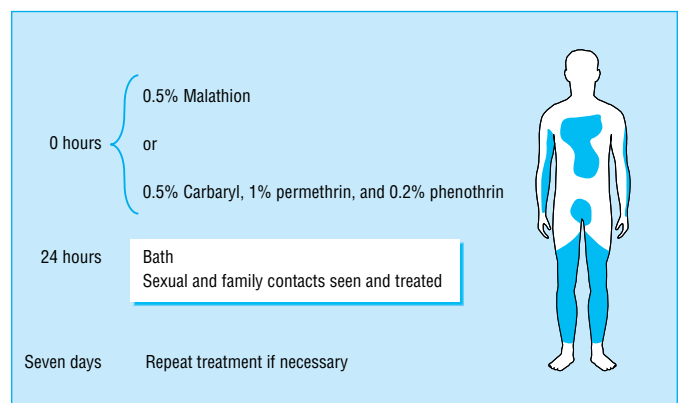
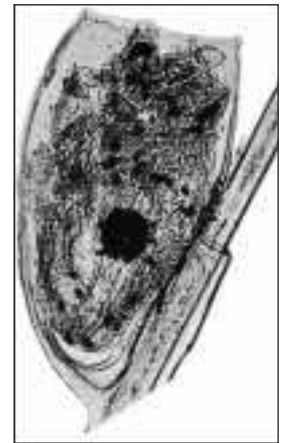
## Scabies

A scabies infestation is caused by the mite *Sarcoptes scabiei*. The clinical features of scabies are caused by the female burrowing in the uppermost layer of the skin (stratum corneum), laying eggs and defecating. The disease and associated symptoms are largely caused by an allergy to intestinal enzymes. The female is about twice the size (0.3mm long) of the male and can just be seen by the naked eye as a black dot (mouth parts) at the distal part of the burrow. Infestation usually occurs as a result of close physical, but not necessarily sexual, contact. Close contact needs to be reasonably prolonged because the insect moves slowly (at 25 mm/minute). Outbreaks of non-sexually acquired scabies may occur among schoolchildren and within whole households or long stay hospitals. Outbreaks are also common in impoverished communities in the tropics.

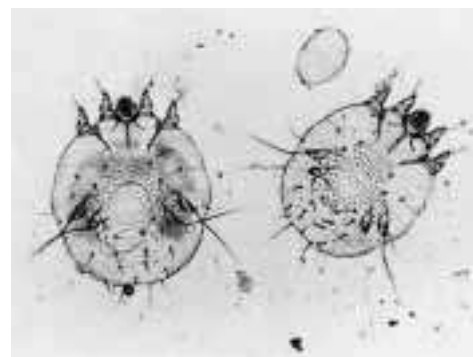
Symptoms are first noticed between two and six weeks after infestation. Reinfection may give rise to symptoms within a few hours. The patient complains of itching, which is often unbearable, intractable, and worse at night, when the body is warm. The sites of itching and burrows bear no relation to the mode of transmission. Thus, lesions may often be found in the clefts of fingers and on the wrists and elbows as well as on the genitals. On examination, the burrows may be the typical sinuous, scaling, reddish grey lesions (5-15 mm long),



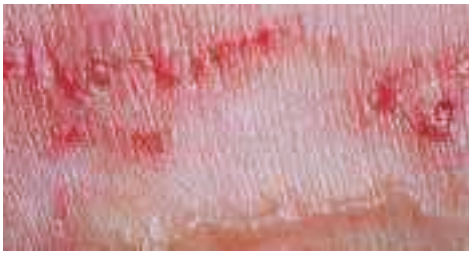
*P pubis*



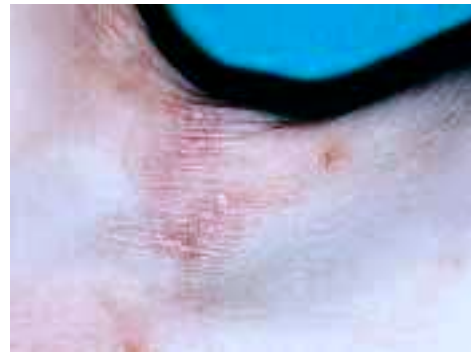
Management of pediculosis pubis



*S scabiei*



Burrow

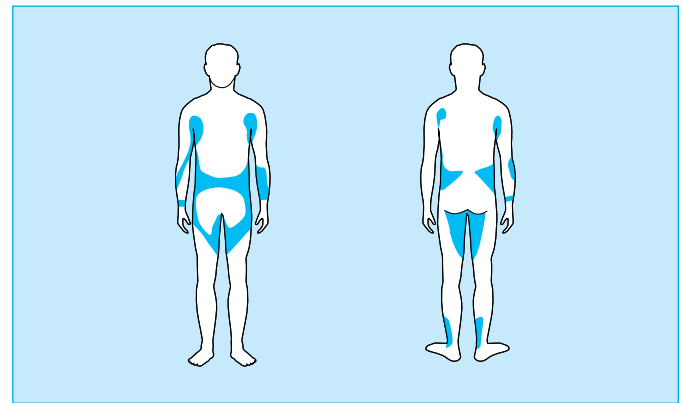


Finger cleft

sometimes with small vesicles at their end. However, scratching may alter their appearance by producing excoriation, ulceration, crusting, and bleeding. The lesions on the penis and scrotum may resemble red papules. Associated rashes are sometimes found in sites distant from the actual burrows, in particular erythematous urticarial papules in the armpits, abdominal wall, and the anterior and posterior aspects of the upper thighs. In some cases, indurated nodules, eczematous changes, and secondary infection with pustule formation may occur.

Diagnosis is based on the clinical history and examination and may be confirmed by finding the mite, eggs, or scybala. This is achieved by scraping the top off the whole length of a burrow (from distal to proximal end) with a scalpel, putting the material on a slide with 10% potassium hydroxide solution, and looking for the mite under the microscope. As with pediculosis pubis, if the history implies sexual transmission then other sexually transmitted infections must be excluded.

Scabies is treated by applying malathion (0.5%) or permethrin (5%) to the whole body and washing it off after 12 hours. Patients should be told that the initial itching may persist for several weeks despite successful treatment with either preparation. Unless this explanation is given, patients may equate the symptoms with continuing infection, re-treat themselves, and run the risk of chemical dermatitis. Sexual contacts should be seen if sexual transmission is suspected. If the condition was not acquired by this route, other members of the family or school friends will need to be treated. When contacts are seen they may be asymptomatic, but they should be treated because they may be incubating the disease. No special treatment of clothing or bed linen is necessary.



Areas affected by scabies infestation

# 15 Viral hepatitis

Richard Gilson

Most cases of acute hepatitis present with jaundice associated with some gastrointestinal and systemic symptoms of recent onset and are caused by one of the hepatitis viruses A to E. The clinical features associated with each infection do not distinguish them, but the history will often give a clue to the aetiology, particularly in relation to sexual or parenteral exposure. Other cases are identified incidentally because of abnormal liver function tests, which may also lead to the diagnosis of chronic viral hepatitis. Hepatitis B and hepatitis C virus infections are often diagnosed at the stage of chronic infection. Some patients only present having developed the late sequelae of chronic viral hepatitis, such as cirrhosis or hepatocellular carcinoma.

**Hepatitis B and hepatitis C virus infections are often diagnosed at the stage of chronic infection**

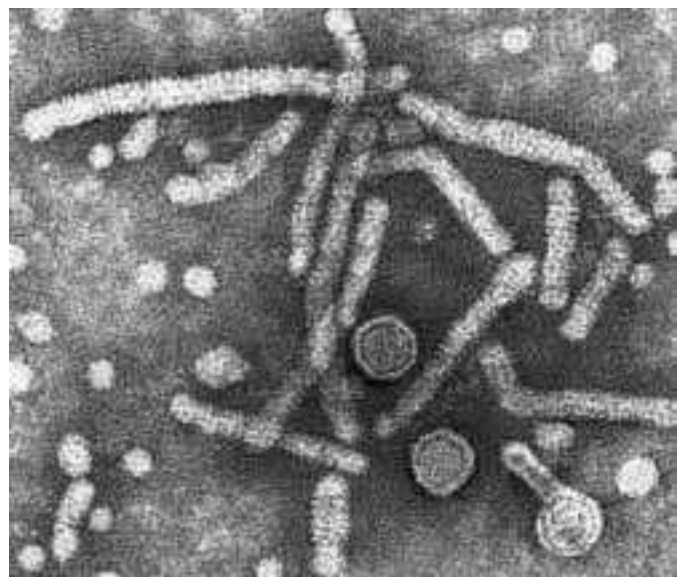
## Comparison of hepatitis virus infections A-E

Hepatitis type	Incubation period	Transmission routes	Carrier state
A	Two to six weeks	Faecal-oral	None
B	8-12 weeks, but up to 24 weeks	Parenteral, perinatal, or sexual (homosexual and heterosexual)	5% adults, 90% infants
C	Four to eight weeks but up to 24 weeks	Parenteral (particularly blood or blood products, if not screened, and injecting drug use) and sexual and perinatal (lower risk)	60-70%
D	Six to eight weeks	Parenteral (coinfection with acute hepatitis B or superinfection of hepatitis B carrier)	About 2% if acute coinfection, 70-80% if superinfection
E	Two to six weeks	Faecal-oral	None

## Causes and epidemiology

Hepatitis A is caused by a small RNA virus that is excreted in the stools for up to two weeks before the onset of symptoms. Hence, transmission is by faecal-oral spread, usually through contaminated food or water in endemic areas. Person to person transmission occurs within households, which may, therefore, include sexual partners. Transmission during sexual contact can occur and has been associated with oral-anal contact. Outbreaks in homosexual men have been reported, but prevalence studies show that sexual transmission contributes little to the risk of hepatitis A in homosexual men. In developing countries, childhood infection remains very common, but in developed countries, the rates of infection have declined so that an increasing proportion of adults are susceptible; for example, only about 20-25% of young adults in London are immune.

Hepatitis B is caused by a small DNA virus that is detectable in serum for several weeks before the onset of acute illness. At the same time a large excess of hepatitis B surface antigen is produced in infected liver cells, which is released in the bloodstream as small spherical or filamentous particles. Patients who fail to clear the infection after six months are persistent virus carriers, some of whom maintain high levels of viraemia and consequently are infectious. Chronic carriers represent the main pool of infectious individuals. In low prevalence regions, including northern Europe, Scandinavia, and North America, the prevalence of hepatitis B virus (HBV) carriers is less than 1% (0.1% in the United Kingdom), and



Electron micrograph of hepatitis B virus particles in serum showing small spheres and filaments comprising hepatitis B surface antigen. Large spherical structures are virus particles that contain hepatitis B core protein and viral DNA. With permission of the Division of Viral Hepatitis at the Centers for Disease Control and Prevention

most infections occur in adults due to sexual or parenteral transmission. Those at greatest risk are homosexual men who practice unprotected anal intercourse and injecting drug users who share any of their injecting equipment. Up to 5% of homosexual men and injecting drug users who attend sexually transmitted infection (STI) clinics in the United Kingdom are carriers and 25-50% are immune because of a previous infection. In many parts of the world, the carrier rate in the general population is much higher, up to 20%, and the highest incidences are found in the perinatal period (because of mother to baby transmission), early childhood, and later in adolescence with the start of sexual activity.

Hepatitis D is caused by a defective RNA virus that needs concurrent infection with hepatitis B virus for the virus to replicate productively. Simultaneous acute infection usually resolves. Superinfection in a hepatitis B carrier causes an exacerbation of any pre-existing chronic hepatitis, which can be severe and leads to persistent dual infection. Hepatitis D is parenterally and sexually transmitted, but injecting drug users are at greater risk than, for example, homosexual men.

The hepatitis C virus was identified in 1989 and is the cause of over 90% of cases of non-A, non-B hepatitis. Historically, the greatest risk of infection with hepatitis C was exposure to untested or untreated blood or blood products and sharing of any injecting equipment by injecting drug users. Since the introduction of blood donor screening (September 1991 in the United Kingdom), infections related to blood or blood products have been almost eliminated. The reuse of needles and other medical equipment is an important source of infection in some countries. Up to 10-20% of patients have no history of parenteral exposure, indicating transmission by person to person or sexual contact. Studies of sexual partners (homosexual and heterosexual) of patients with hepatitis C found a low prevalence of infection. These data are consistent with a low rate of transmission of hepatitis C by sexual contact. Vertical transmission occurs at a low rate, about 5%.

Hepatitis E, caused by a small RNA virus, is the principal cause of the enterically transmitted form of non-A, non-B hepatitis. Spread by the faecal-oral route, the hepatitis E virus causes sporadic cases and waterborne epidemics in the Indian subcontinent, South East and Central Asia, Africa, and North America. In Europe, cases are only likely to be seen in travellers who return from these regions. Like hepatitis A, no carrier state exists, and sexual transmission has not been implicated.

Other causes of viral hepatitis are more speculative, and none are believed to be important causes of sexually acquired hepatitis. Hepatitis F has yet to be characterised. The hepatitis G virus was believed to be another cause of non-A, non-B hepatitis. Structurally related to hepatitis C, it is transmitted in blood or blood products and is often found in association with hepatitis C. However, it now seems that hepatitis G rarely, if ever, causes liver disease.

## Clinical evaluation

Most cases of acute hepatitis diagnosed in primary care and in STI clinics are caused by infection with either hepatitis A or B. A history of travel, injecting drug use, tattoos, recent transfusion, or other percutaneous exposure may provide clues to the diagnosis. However, it is also important to ask about sexual orientation and household or sexual contacts and whether they have had symptoms of hepatitis. Hepatotoxins such as alcohol and drugs should be excluded as a cause of liver disease. No major differences are seen in the clinical features of the acute

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### Groups at risk of infection with hepatitis B

#### Endemic areas

- Whole population (peak incidence in neonates, early childhood, and adolescence)

#### Areas of low endemicity (for example, United Kingdom)

- Babies born to hepatitis B carrier mothers
  - Homosexual men
  - Injecting drug users
  - Prostitutes
  - Sexual contacts of acute cases and carriers
  - Household contacts of acute cases and hepatitis Be antigen positive carriers
  - Laboratory and medical staff exposed to blood or blood products
  - Staff and inmates of closed institutions
- 

**Hepatitis D is rare in the United Kingdom but has been reported in up to 14% of carriers of hepatitis B virus in southern Europe**

**In studies of homosexual men, the prevalence of hepatitis C, typically about 1%, is much lower than that of hepatitis B or HIV, although this may still be higher than in heterosexual controls**

**TT virus (named after the patient from whom it was isolated) is another infection linked to blood or blood product exposure. Other viral infections that can be sexually acquired and may cause hepatitis include cytomegalovirus and Epstein-Barr virus**

**The clinical illness associated with acute hepatitis begins with non-specific symptoms, such as fever, headache, and fatigue, followed by jaundice. More than half of all acute infections are subclinical**



## ABC of Sexually Transmitted Infections

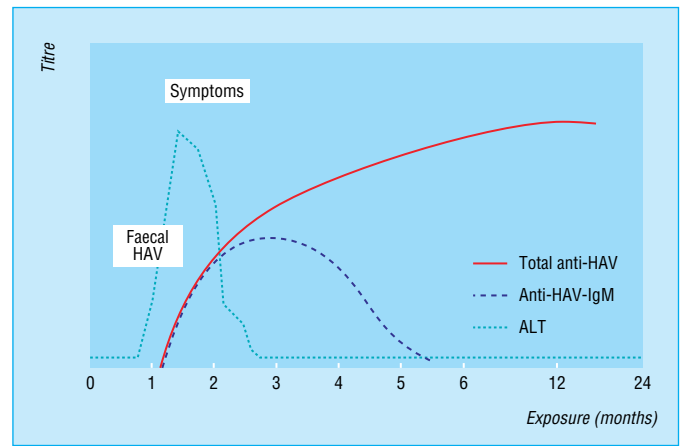
illness caused by any of the hepatitis viruses. In addition, chronic hepatitis B or C cannot be distinguished clinically. Occasionally, extrahepatic manifestations, such as cryoglobulinaemia associated with hepatitis C, may be present. Symptoms and signs of other concurrent STIs should be looked for.

### Diagnostic tests

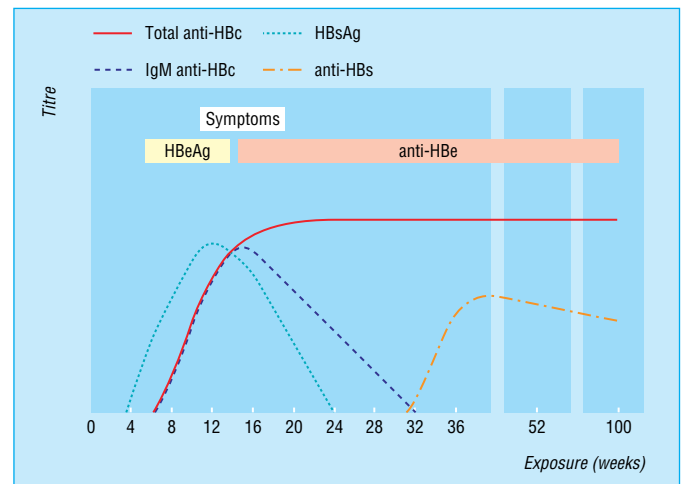
Virological diagnosis relies on serological tests. Routine liver function tests help to distinguish between hepatitis and cholestasis caused by extrahepatic or intrahepatic lesions, but prolonged cholestasis occurs occasionally with acute viral hepatitis. Tests of synthetic function, such as prothrombin time and serum albumin, are useful to assess the severity of both acute and chronic hepatitis.

A patient who has had hepatitis A at any time in the past will have antibodies that can be detected by a test for total anti-hepatitis A virus (HAV). A patient with acute hepatitis A will also have antibodies that are picked up by a class-specific test for anti-HAV immunoglobulin M (IgM) antibodies. These remain detectable for three to four months after the acute episode.

Acute hepatitis B can be diagnosed by the presence of IgM antibodies to the hepatitis B core (anti-HBc IgM). Hepatitis B surface antigen (HBsAg) is detectable during the acute illness, often before any antibody response or rise in transaminase has occurred. Patients with acute hepatitis B who resolve their infection usually clear HBsAg from their serum within a few weeks. Occasionally, detectable HBsAg is lost even before the patient becomes symptomatic. In these cases, the diagnosis is made by tracing the evolution of the anti-HBc IgM response and the appearance of antibodies to HBsAg (anti-HBs). After the clearance of detectable serum HBsAg, a delay of a few weeks or months may occur before anti-HBs can be detected, which is the best marker of immunity to the hepatitis B virus. By definition, patients who remain HBsAg positive after six months are persistent virus carriers. One additional serological marker is the hepatitis Be antigen (HBeAg), which is a soluble, truncated form of the core protein and the corresponding antibody (anti-HBe). HBeAg can be detected during acute infection but disappears quickly in those individuals who do not become carriers. The detection of HBeAg is associated with other measures of virus replication such as hepatitis B virus DNA in the blood. Carriers who are HBeAg positive are much more likely to transmit infection during sexual contact or from mother to baby at birth. They are also more likely to experience progression of chronic liver disease.



Hepatitis A: typical serological course. HAV = hepatitis A virus; IgM = immunoglobulin M; ALT = alanine aminotransferase



Hepatitis B: typical serological course of resolving acute infection. HBc = hepatitis B core. HBsAg = hepatitis B surface antigen. Anti-HBs = antibody to hepatitis B surface antigen. IgM = immunoglobulin M. HBeAg = hepatitis Be antigen. HBe = hepatitis Be

### Hepatitis B serology: interpretation of common patterns of results

	HBsAg	Anti-HBs	Anti-HBc	Anti-HBc-IgM	HBeAg	Anti-HBe
Never infected	-	-	-			
Immune after a course of vaccine	-	+	-			
Immune after a natural infection	-	+	+			
Acute infection						
Early or pre-symptomatic	+	-	-	-	+/-	-
Late or symptomatic	+	-	+	+	+	-
Chronic infection						
High infectivity	+	-	+	+/-	+	-
Low infectivity	+	-	+	-	-	+

HBsAg = hepatitis B surface antigen; Anti-HBs = antibody to hepatitis B surface antigen; anti-HBc = antibody to hepatitis B core; IgM = immunoglobulin M; HBeAg = hepatitis Be antigen; anti-HBe = antibody to hepatitis Be antigen

Screening for hepatitis C is done with an antibody test. The sensitivity and specificity of current assays is much higher than the first generation of tests developed in the early 1990s. The early tests relied on a single recombinant protein from a non-structural region of the virus. Current assays incorporate additional peptides from the nucleocapsid and envelope regions. With these tests, acute hepatitis C can be diagnosed at the time of presentation, although the antibody response may be delayed for up to four weeks and diagnosis of an acute infection then relies on detecting the hepatitis C virus genome with a polymerase chain reaction or signal amplification assay. These assays are also used in patients with detectable antibodies to determine whether they have persistent viraemia. The presence of antibodies alone does not distinguish individuals who are currently infected from those who may have cleared their hepatitis C virus (HCV) infection, although this only occurs in 30-40% of infected individuals. Finally, assays for HCV RNA can be used as quantitative measures of viral load for monitoring treatment. Tests for the hepatitis C virus genotype are available and are used when considering treatment for chronic hepatitis C, genotype being the strongest predictor of response.

Hepatitis D and E are diagnosed by antibody assays. Hepatitis D can be diagnosed only in a patient with serological markers of hepatitis B. Immunoglobulin M antibody tests help to distinguish between acute and chronic infections. In patients with hepatitis that may have been acquired sexually, screening for other STIs including HIV and syphilis should always be considered.

### Natural course of viral hepatitis

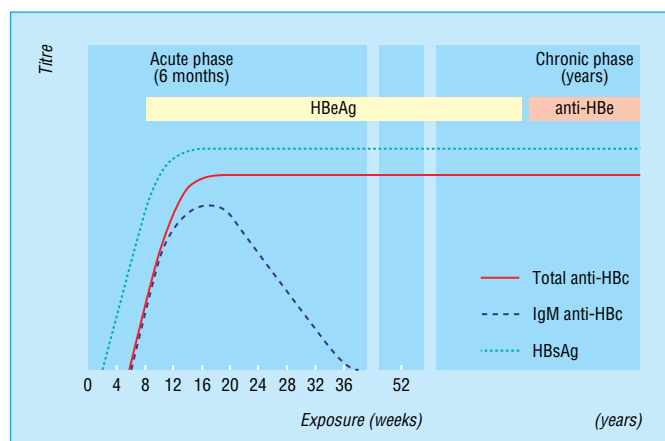
Most cases of hepatitis A are asymptomatic, but the risk of severe disease, including fulminant hepatic failure, increases with age and in those with concurrent chronic liver disease. No carrier state exists for hepatitis A and immunity is lifelong. As the incidence of hepatitis A in childhood falls, a higher proportion of cases will occur in adults and, therefore, be symptomatic.

Up to 90% of neonates infected with hepatitis B become chronic carriers, the proportion falling rapidly with age up to five years. Thereafter, about 5% of patients with acute hepatitis B become carriers, but fewer if the acute infection is symptomatic. Fulminant hepatitis occurs in less than 1% of cases and never leads to chronic infection. Initially, chronic carriers have high amounts of viral replication, with HBeAg detectable in the serum. The rate of viral replication falls with time, and most patients will seroconvert spontaneously from HBeAg positive to anti-HBe positive. This occurs at a rate of about 10% per year of follow up. Chronic hepatitis B carriers with anti-HBe typically have little inflammatory liver disease and their risk of developing more severe disease is low. Those in whom HBeAg to anti-HBe seroconversion is delayed are more likely to progress to cirrhosis and end stage liver disease. Cirrhosis also is associated with an increased risk of primary hepatocellular carcinoma.

The clinical course of chronic hepatitis C is similar to that of chronic hepatitis B. The proportion of individuals who develop clinically important liver disease is uncertain (estimated to be 10-30%), but it rarely occurs within 10 years of infection. The average time to the development of cirrhosis is 30-40 years. Those who do not develop chronic infection may lose detectable antibodies.

## HIV coinfection

Concomitant infection with hepatitis B or hepatitis C and HIV is common. Interactions between hepatitis B and HIV include an increase in the proportion of those infected people who



Hepatitis B: typical serological course of chronic infection. HBc = hepatitis B core; IgM = immunoglobulin M; HBsAg = hepatitis B surface antigen; HBe = hepatitis Be; HBeAg = hepatitis Be antigen

**Some patients with anti-HBe carry viruses with mutations in the hepatitis B pre-core or core promoter gene sequence. These patients are more likely to have detectable viraemia and have an intermediate risk of progression to end stage liver disease**

**Acute infection with hepatitis C virus is rarely symptomatic (10%), but it becomes chronic in about 60-70% of cases; the exact proportion is uncertain and may depend on the route of transmission**

## ABC of Sexually Transmitted Infections

become HBV carriers to about 20%, higher HBV replication, and a reduction in the rate of spontaneous HBeAg to anti-HBe seroconversion. Infection with HIV may also lead to reactivation of HBV infection. The effect on the epidemiology of HBV infection is to increase the pool of infectious carriers. Although the activity of HBV associated inflammatory liver disease may be reduced in the early stages of HIV coinfection, cases of rapidly progressive liver disease are seen; in cohort studies, mortality is still determined largely by other HIV related complications.

HIV coinfection can accelerate the progression of HCV related chronic liver disease, as well as increasing the HCV viral load. It increases the risk of mother to child transmission and may also increase the risk of sexual transmission.

## Management

Acute viral hepatitis is usually self limiting and management is largely supportive. Most patients can be managed in the community, but acute liver failure and its complications demand urgent hospital admission. In uncomplicated cases, a low fat, high energy diet is more palatable and bed rest advisable during the early phase of the illness. Usual advice is to avoid alcohol until the liver function tests are normal.

The prospects for treatment for both chronic hepatitis B and C have improved. Treatment of hepatitis B with interferon  $\alpha$  for four to six months results in 20–40% loss of HBeAg, depending upon the pre-treatment characteristics. Predictors of response include a lower serum HBV DNA concentration, higher transaminase activity, and more inflammatory disease on liver biopsy, although these also predict a higher rate of spontaneous seroconversion of HBeAg to anti-HBe. Treatment with lamivudine, a nucleoside analogue, has the advantage of being an oral therapy that is much better tolerated. Sustained HBeAg seroconversion occurs in only 10% of patients, and viral resistance develops in most patients who are given long term therapy. Adefovir, a nucleotide analogue, recently has been licensed in the United States and Europe and has similar efficacy to lamivudine but with a much lower incidence of resistance. It is effective against lamivudine resistant and pre-core mutant infections and improves the liver histology in patients with anti-HBe and active liver disease. Current treatments are not indicated for carriers with anti-HBe and normal biochemical and histological findings, although they still have a small excess risk of developing chronic liver disease.

Chronic hepatitis C may also respond to interferon  $\alpha$  therapy; however, combination treatment with oral ribavirin improves the response rate. The recommended treatment duration is six months for HCV genotype 2 or 3 and 12 months for other types. New forms of pegylated interferon have longer half lives that allow once weekly, rather than three times weekly, dosing, and improve the response rate, particularly for genotype 1.

## Screening and prevention

The transmission of hepatitis A can be prevented by applying simple precautions to reduce faecal-oral contamination. Recent sexual contacts of acute cases can be protected by passive immunisation with human normal immunoglobulin within 14 days. Hepatitis A vaccine provides protection when given within seven days of exposure and, with a booster dose at 6–12 months, will provide long term immunity. Immunisation of homosexual men whose sexual behaviour places them at risk has been recommended, but those at risk are not well defined. Routine prophylaxis of all homosexual men is not currently

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### Interactions between infection with HIV and hepatitis B virus

- Incidence of fulminant hepatitis—possibly decreased
  - Incidence of carrier state after infection—increased
  - Infectivity of HBV carriers—increased
  - Hepatic inflammatory activity—decreased in early disease
  - Response rate to vaccine—decreased
  - Loss of natural and vaccine induced immunity—increased
  - Response to antiviral treatment—decreased (but some antiretroviral agents also have anti-HBV activity)
  - Risk of cirrhosis and hepatocellular carcinoma—possibly increased
- 

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### Indications for admission to hospital with acute hepatitis

#### Complications

- Symptoms and signs of acute liver failure (signs of hepatic encephalopathy)

#### Doubts about the diagnosis

- Possible extrahepatic cause for jaundice

#### Social factors

- Patient living alone
- 

**Although treatment should be considered for HBV carriers, the efficacy is still poor for a large group of patients, particularly in regions of high endemicity where patients are HBeAg positive but have normal liver function**

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### Prevention of hepatitis as a sexually transmitted disease

- Contact tracing
  - Counselling of HBeAg positive carriers
  - Passive immunisation
    - Hepatitis A—normal human immunoglobulin
    - Hepatitis B—hepatitis B immunoglobulin (HBIG)
  - Active immunisation—vaccine
    - Hepatitis A—in outbreak situations in homosexual men
    - Hepatitis B—targeted immunisation
  - Safer sex or barrier contraception
    - Hepatitis C (no vaccine available)
    - Hepatitis A (avoid oral-anal exposure)
-

recommended. The main groups to be offered vaccine routinely are travellers and patients with chronic liver disease, the latter because of an increased risk of adverse outcomes. Currently, more widespread screening is not indicated in either primary care or STI clinics.

Hepatitis B transmission to carers and other contacts can be limited by careful handling of blood, blood contaminated material, and instruments; however, those at risk should be given vaccine. Sexual and household contacts of patients with acute hepatitis B should be traced and offered vaccine. If seen within 72 hours of an isolated sexual or parenteral exposure, hepatitis B immunoglobulin can be given as additional passive prophylaxis. Tracing the contacts of a case of acute hepatitis B may identify the source, who is usually an HBeAg positive carrier. Source contacts can be counselled about their infectivity and protection of other non-immune sexual contacts and be offered further assessment and treatment. In most parts of the world, programmes of universal infant immunisation against hepatitis B have been established, sometimes with “catch up” immunisation of adolescents. In the United Kingdom, the strategy is still for targeted immunisation. Current British recommendations on screening apply equally to primary care and STI clinics and include gay and bisexual men, injecting drug users, contacts of individuals with acute or chronic hepatitis B, and sex workers. Those who are not already immune should be given vaccine. In addition, individuals from high prevalence countries should be screened to identify hepatitis B carriers who may be at risk of infecting others, as well as being candidates for treatment.

Current hepatitis B vaccines contain a recombinant hepatitis B S-protein. In some parts of the world, plasma derived vaccines are still used. Both types of vaccine are safe and protect over 90% of immunocompetent vaccinees for at least five years. The standard course is three doses at zero, one, and six months, or four doses at zero, one, two, and 12 months. More rapid vaccine courses, for example zero, seven, and 21 days, have been proposed. These produce protective concentrations of anti-HBs antibody sooner, but the titre is low and the long term efficacy is uncertain without a booster at six or 12 months. Vaccines containing preS1 and preS2 proteins may overcome a non-response to the standard vaccine and produce an equivalent response with only two doses, but none are yet available in the United Kingdom.

In low prevalence countries, such as the United Kingdom, the hepatitis B vaccine policy is to target those most at risk, whereas in most countries, universal immunisation of infants or adolescents (or both initially) is being implemented. In a targeted strategy, and depending upon the prevalence, savings can be made by pre-vaccine testing for HBV markers. Post-vaccine testing to confirm a response (or detect current infection if not excluded by pre-vaccine screening) is advised. Non-responders or poor responders may benefit from further doses of vaccine. The need for routine booster doses is questionable. Booster doses are not cost effective at a population level.

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## Overview of hepatitis B and C

### Importance

Hepatitis B and C are the main causes of chronic viral hepatitis (defined as viral persistence for more than six months) and occurs in 5% of cases of hepatitis B in adults and 60-70% cases of hepatitis C. Both may lead to liver fibrosis, cirrhosis, and liver failure or hepatocellular carcinoma

### Virology

Hepatitis B is a DNA virus; hepatitis C is an RNA virus. Diagnosis is by serology. Screening tests for hepatitis B are for HBsAg, anti-HB core, and anti-HB surface; hepatitis C tests are for anti-HCV and HCV RNA (both are detectable in persistently infected patients)

### Transmission

Both hepatitis B and C are spread by parenteral, sexual, and mother to baby exposure. Cases of acute hepatitis B and HBeAg positive carriers are the most infectious by all routes. Parenteral exposure is a much greater risk than vertical or sexual exposure for hepatitis C

### Symptoms and presentation

Most cases of acute hepatitis are asymptomatic, but all types of acute viral hepatitis may present similarly with fever, headaches, and fatigue before jaundice is seen. Most cases of hepatitis B and C are diagnosed only during the chronic phase as a result of screening or investigation of abnormal liver function tests

### Treatment

No specific treatment is available for acute hepatitis B or C. Individuals with chronic hepatitis B who have active virus replication and liver disease can be treated with interferon, lamivudine, or adefovir. Treatment for hepatitis C with interferon or ribavirin is recommended with similar indications

### Prevention

A vaccine is available for hepatitis B; no specific prophylaxis has been developed yet for hepatitis C

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**Recent evidence shows that after hepatitis B vaccination most patients will be protected for at least 15 years. HIV positive and other immunosuppressed patients may not be protected as effectively and may need booster doses when anti-HBs titres drop below 100 IU/l**

# 16 HIV

Ian G Williams, Ian Weller

HIV was first detected in 1983 in a patient with AIDS. Serological tests for antibodies to HIV infection were subsequently developed in 1984, and the natural course of HIV infection was characterised in prospective cohort studies in the 1980s. Chronic HIV infection over several years results in progressive damage to the immune system, which leads to severe immune deficiency, opportunistic infections, cancers, and death. In recent years, marked improvements have been made in treatments, resulting in dramatic decreases in the incidences of AIDS and death in the developed world. HIV and AIDS remains, however, a major cause of mortality and morbidity in the developing and other parts of the world. The classification and staging of HIV disease have been defined by the Centers for Disease Control (CDC) in the United States and the World Health Organization (WHO). The CDC system is used widely in the developed world, and the WHO system is used in the developing world.

## Epidemiology

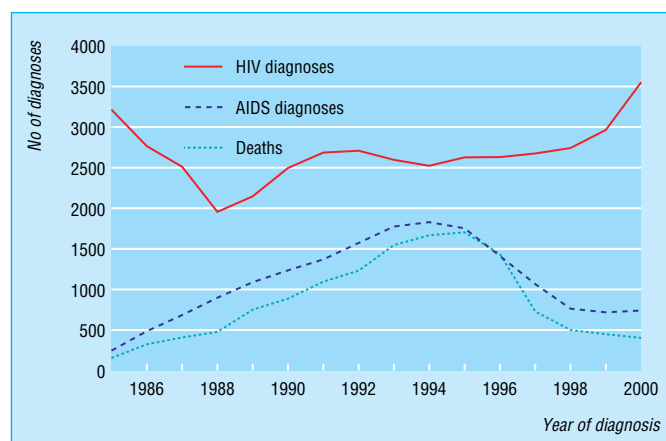
HIV is transmitted sexually, in blood or blood products, and perinatally. The number of reported cases continues to increase; by the end of 2001, the United Nations estimated that 40 million adults and children worldwide were living with HIV and AIDS, of whom 28.5 million were in living in sub-Saharan Africa. In the UK by June 2002, 51 081 cases of HIV infection had been reported. Within the developed world, most of those infected are men (79% in the United Kingdom and 54% in the United States), of whom the majority are either homosexual or injecting drug users. Most of the affected women are either injecting drug users, have had sexual contact with injecting drug users or bisexual men, or are from countries where heterosexual transmission is a prominent risk factor. Paediatric cases usually occur as a result of the mother having AIDS or belonging to a group at risk of acquiring AIDS.

In patients newly diagnosed every year, the proportion that is heterosexual has increased. In the United Kingdom and the United States, more than 50% are heterosexual. In the United States this largely reflects the epidemic among intravenous drug users, whereas in the United Kingdom the increase reflects acquired HIV infection in Africa. Worldwide heterosexual intercourse is the main route of transmission. In sub-Saharan Africa and South and South East Asia, the ratio of infected men to infected women is virtually 1:1.

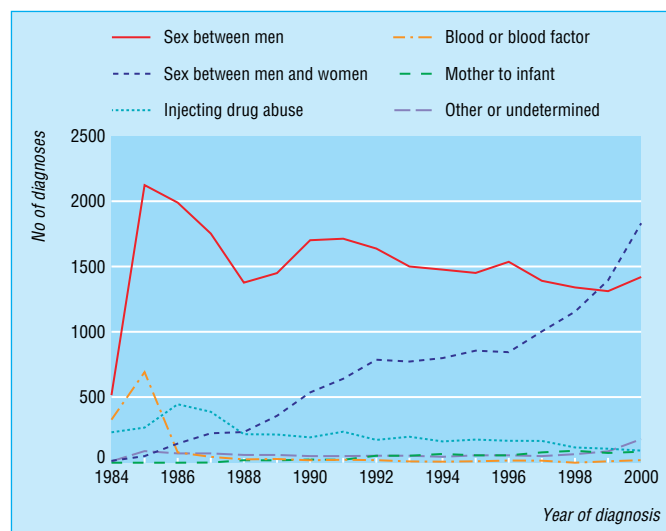
Since 1996 in the developed world, both the incidence of new cases of AIDS and the mortality have fallen dramatically as a result of the use of highly active antiretroviral therapies (HAART). Reducing the prevalent population of undiagnosed cases of HIV infection, earlier diagnosis, and improved access to care are essential for further reducing the incidence of AIDS and AIDS related death. In the United Kingdom 30% of the total population infected with HIV are estimated to remain undiagnosed, and a high proportion of these are black African heterosexual men and women, who are more likely to be diagnosed in advanced disease or with an AIDS defining illness compared with other affected groups.

Centers for Disease Control revised classification system for HIV infection, 1993

CD4 + T cell categories	Clinical categories		
	Asymptomatic, acute (primary) HIV or PGL	Symptomatic, not (A) or (C) conditions	AIDS indicator conditions
$\geq 500 \times 10^6 / l$	A1	B1	C1
$200-499 \times 10^6 / l$	A2	B2	C2
$< 200 \times 10^6 / l$	A3	B3	C3



HIV diagnoses, AIDS case reports, and deaths in HIV infected individuals in the United Kingdom, by year of diagnosis or occurrence. Adapted from slide from the Health Protection Agency website ([www.hpa.org.uk](http://www.hpa.org.uk)). Data from Communicable Disease Surveillance Centre, Scottish Centre for Infection and Environmental Health, and the Institute of Child Health



Reports to Communicable Disease Surveillance Centre of all HIV infected individuals by year of diagnosis. Adapted from slide from the Health Protection Agency website ([www.hpa.org.uk](http://www.hpa.org.uk)). Data from Communicable Disease Surveillance Centre, Scottish Centre for Infection and Environmental Health, and the Institute of Child Health

## Immunology

Depletion and impaired function of the T helper lymphocyte subset (lymphocytes bearing the CD4 cluster differentiation antigen) is the primary abnormality of immune dysfunction. The CD4 molecule, however, is also displayed at lower density on other cells, such as monocytes, macrophages, and some B lymphocytes. The CD4 lymphocyte has a pivotal role in the immune response (interacting with macrophages, other T cells, B cells, and natural killer cells, either by direct contact or by the influence of lymphokines such as interferon  $\gamma$  and interleukin 2). The mechanism for CD4 lymphocyte loss remains uncertain, but probably includes enhanced apoptosis (programmed cell death) and inhibition of CD4 lymphocyte growth.

## The virus

HIV has a cylindrical core and its nucleic acid has been cloned and sequenced. It has a basic gene structure common to all retroviruses, but it is very different from the other human retroviruses (human T lymphotropic viruses I and II). The CD4 antigen is a major component of the viral receptor required for cell entry. Only cells bearing this antigen are susceptible to infection. The  $\beta$  chemokine receptors (CCR5 and CXCR4) also act as coreceptors for HIV entry and their expression of the cell surface determines the susceptibility of CD4 bearing cell lines to different HIV strains.

On entry to the infected cell, the viral reverse transcriptase enzyme (hence retrovirus) makes a DNA copy of the RNA genome (proviral DNA). The proviral DNA is able to integrate into the host cell DNA. Latent, non-productive, or productive viral replication may occur. During productive replication, RNA, transcripts are made from the proviral DNA, and complete virus particles are assembled and released from infected cells by characteristic budding.

## Natural course

### Acute infection

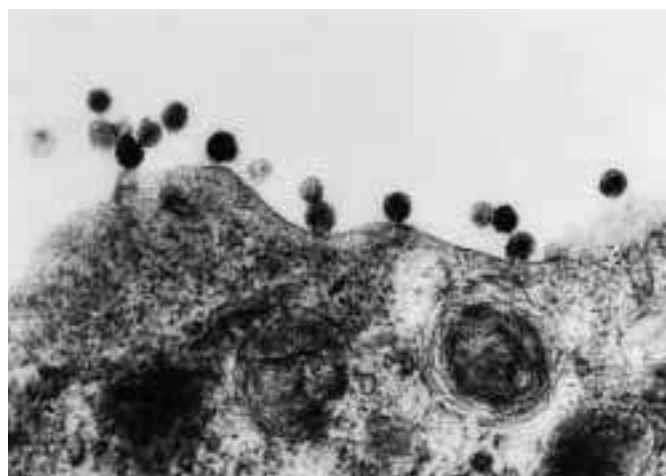
Acute infection with HIV may be accompanied by a transient non-specific illness similar to glandular fever; it includes fever, malaise, myalgia, lymphadenopathy, pharyngitis, and a rash. A transient aseptic meningoencephalitis may also occur. Most acute infections, however, are subclinical. The acute infection is accompanied by the development of antibodies to the core (p24) and surface (GP 41, 120, 160) proteins, usually in two to six weeks, although delayed seroconversions have been observed. Antibodies usually are detected by enzyme linked immunoassays, and their presence can be confirmed by immunofluorescence or western blotting.

Initial concentrations of plasma viraemia detected by polymerase chain reaction are very high but then decline rapidly within a few days to weeks as the immune response to HIV develops. It is not clear which immune mechanisms are primarily responsible for this initial fall in viraemia, but the breadth and strength of HIV specific CD4 and CD8 T cell responses that develop during primary infection are important for long term virological control in chronic HIV infection.

The effectiveness of these specific immune responses determines the efficacy of virological control and, thus, plasma viraemia. A high plasma RNA concentration is associated with a more rapid decline in CD4 count over time and a quicker progression to symptomatic disease, whereas a very low concentration is predictive of slow or non-progression. The efficacy of the immune response in acute primary infection,

### Range of immune dysfunction

- $\downarrow$  T helper cells (CD4+)
- Expansion of CD8 cells and impairment of cytotoxic T cell responses
- Depletion of T cell antigen repertoire
- $\uparrow$  immunoglobulins: polyclonal B cell activation,  $\downarrow$  de novo antibody response



Electron micrograph of virus. Properties: retrovirus, two strands of RNA (100-120 nm diameter); genes are gag (core proteins), pol (polymerase or reverse transcriptase), env (envelope proteins), and accessory genes that regulate viral protein synthesis and replication; wide genomic diversity, most pronounced in env region. CD4 tropism; cytopathic effect in susceptible cell lines; latency; antibodies to core and envelope proteins (weak neutralising activity)

**Diagnosis of acute HIV infection is confirmed by a positive virus detection assay (plasma HIV RNA, cellular proviral DNA, or p24 antigen) in the presence of a negative or evolving (rising titre) antibody profile**

## ABC of Sexually Transmitted Infections

therefore, seems to determine a “set point” for which viral application is controlled over time.

### Chronic infection

In the early stages chronic infection is asymptomatic. Physical examination may show no abnormality, but about one third of patients have persistent, generalised lymphadenopathy (nodes of 1 cm or more in diameter in two or more non-contiguous extrainguinal sites that cannot be explained by any other infection or condition). The commonest sites of lymphadenopathy are the cervical and axillary lymph nodes; it is unusual in the hilar lymph nodes. Biopsy usually shows a benign profuse follicular hyperplasia.

Later in infection, as the CD4 count declines, non-specific constitutional symptoms develop, which may be intermittent or persistent and include fevers, night sweats, diarrhoea, and weight loss. Patients may also have several “minor” opportunistic infections or conditions that tend to affect the mucous membranes and skin, such as oral candidiasis, oral hairy leucoplakia, herpes zoster, recurrent oral or anogenital herpes simplex, and other skin conditions such as seborrhoeic dermatitis, folliculitis, impetigo, and tinea infections. This collection of symptoms and signs, which are often a prodrome to the development of major opportunistic infection or tumour, is called asymptomatic non-AIDS (CDC stage B).

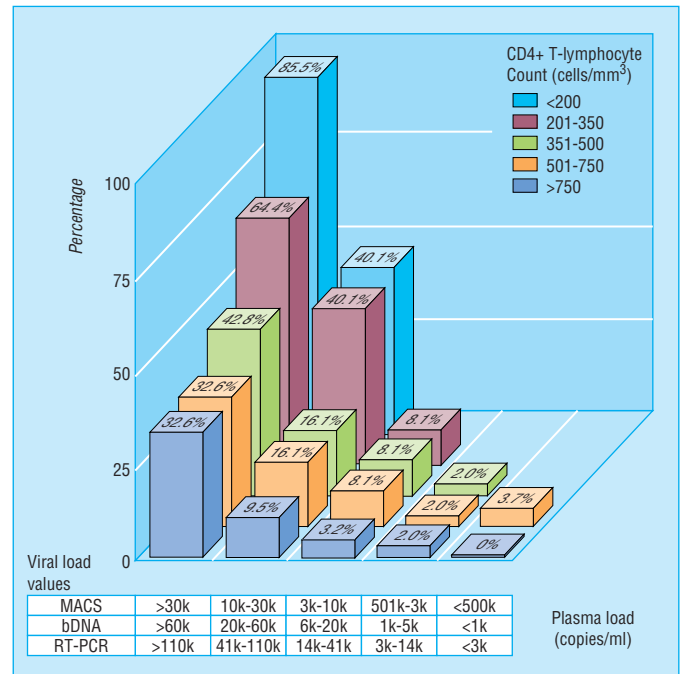
A high plasma viral RNA concentration, CD4 count  $<200 \times 10^6/l$ , and the presence of stage B symptoms are associated with an increased risk of progression to an AIDS defining illness. Clinical monitoring of the CD4 count, plasma HIV RNA concentrations, and stage B symptoms determines when to start antiretroviral therapy to prevent clinical disease progression.

## AIDS

AIDS is defined as an illness characterised by one or more indicator diseases. In the absence of another cause of immune deficiency and without laboratory evidence of HIV infection (if the patient has not been tested or the results are inconclusive), certain diseases when definitely diagnosed indicate AIDS. Regardless of the presence of other causes of immune deficiency, if there is laboratory evidence of HIV infection, other indicator diseases that require a definitive, or in some cases only a presumptive, diagnosis also constitute a diagnosis of AIDS.

### Diseases diagnostic of AIDS without laboratory evidence of HIV

- Candidiasis—oesophageal, pulmonary
- Cryptococcosis—extrapulmonary
- Cytomegalovirus disease—disseminated
- Cryptosporidiosis—diarrhoea that persists for more than one month
- Herpes simplex virus infection
- Mucocutaneous ulceration that lasts more than one month
- Pulmonary, oesophageal infection
- Kaposi's sarcoma—patient younger than 60 years
- Primary cerebral lymphoma—patient younger than 60 years
- Lymphoid interstitial pneumonia—child younger than 13 years
  - *Mycobacterium avium*—disseminated
  - *Mycobacterium kansasii*—disseminated
- *Pneumocystis carinii* pneumonia
- Progressive multi-focal leukoencephalopathy
- Cerebral toxoplasmosis



Likelihood of developing AIDS within three years by CD4 and viral load (bDNA = branched DNA; MACS = Multicenter AIDS Cohort Study; RT-PCR = reverse transcriptase polymerase chain reaction). Adapted from Mellors et al. *Ann Intern Med* 1997;126:946-54

**From cohort studies, it is estimated that without therapy about 75% of HIV infected people can be expected to develop symptomatic (CDC stage B and C) disease within 9-10 years of primary infection**

### Diseases diagnostic of AIDS if laboratory evidence of HIV exists

- Recurrent or multiple bacterial infections—child aged under 13 years
- Candidiasis—pulmonary
- Candidiasis—oesophageal\*
- Cervical carcinoma—invasive
- Coccidioidomycosis—disseminated
- Cryptococcosis—pulmonary
- Cryptosporidiosis—with diarrhoea persisting for more than one month
- Cytomegalovirus retinitis\*
- Cytomegalovirus disease—not in liver, spleen, or nodes
- HIV encephalopathy
- Herpes simplex virus infection—mucocutaneous ulceration that lasts for more than one month or pulmonary, oesophageal infection
- Histoplasmosis—disseminated
- Isosporiasis—with diarrhoea that persists for more than one month
- Kaposi's sarcoma\*
- Lymphoid interstitial pneumonia—child younger than 13 years\*
- Non-Hodgkin's lymphoma—Burkitt's or immunoblastic
- Primary cerebral lymphoma
- Disseminated mycobacteriosis—for example *Mycobacterium avium*\*
- Mycobacterial tuberculosis—extrapulmonary, pulmonary\*
- *P. carinii* pneumonia\*
- Recurrent pneumonia within a 12 month period\*
- Progressive multi-focal leukoencephalopathy
- Salmonella septicaemia—recurrent
- Wasting syndrome due to HIV

\*These indicator diseases may be diagnosed presumptively

### WHO's AIDS case definition for AIDS surveillance

For the purposes of AIDS surveillance, an adult or adolescent (older than 12 years of age) is considered to have AIDS if at least two of the following major signs are present in combination with at least one of the minor signs listed below and if these signs are not known to be caused by a condition unrelated to HIV infection.

#### Major signs

- Weight loss  $\geq 10\%$  of body weight
- Chronic diarrhoea for more than one month
- Prolonged fever for more than one month (intermittent or constant)

#### Minor signs

- Persistent cough for more than one month\*
- Generalised pruritic dermatitis
- History of herpes zoster
- Oropharyngeal candidiasis
- Chronic progressive or disseminated herpes simplex infection
- Generalised lymphadenopathy

The presence of generalised Kaposi's sarcoma or cryptococcal meningitis is sufficient for the diagnosis of AIDS for surveillance purposes.

\* For patients with tuberculosis, persistent cough for more than one month should not be considered as a minor sign

In 1993, the CDC extended the definition of AIDS to include all people who are severely immunosuppressed (CD4 count  $< 200 \times 10^6/l$ ) irrespective of the presence or absence of an indicator disease. For surveillance purposes this definition has not been accepted within the United Kingdom and Europe. In these countries, AIDS continues to be a clinical diagnosis by one or more of the indicator diseases.

In most developing countries, sophisticated laboratory investigations usually are not available. For this reason, the WHO introduced a clinical case definition that could be used for epidemiological surveillance in settings where laboratory facilities are inaccessible. In 1994, this case definition was expanded to incorporate HIV serology and to take into account the revisions to the CDC's case definition. If serological testing is unavailable, the clinical case definition should be used; if serological testing is available, the expanded case definition should be used.

The frequency of specific AIDS defining illnesses differs between the developed and the developing world. In the developed world, pneumocystis pneumonia remains the most common AIDS defining opportunistic infection and non-Hodgkin's lymphoma is accounting for an increased proportion of first AIDS cases. In the developing world, tuberculosis is by far the most common opportunistic infection, together with diarrhoeal disease and wasting syndrome.

## Tumours

### Kaposi's sarcoma

Kaposi's sarcoma is the most common neoplasm that occurs in patients with AIDS, although the incidence has fallen over recent years. It is more common in homosexual men than in the other at risk groups. Before the era of HAART, the median survival time was about two years, although death usually is caused by a supervening life threatening opportunistic infection. The Kaposi's sarcoma of AIDS differs from classic Kaposi's sarcoma, in that widespread skin, mucous membrane (particularly the oral cavity and palate), visceral, and lymph node disease occurs. Visceral, particularly gastrointestinal, lesions are present in as many as half of all patients at presentation.

Nodules of Kaposi's sarcoma also occur in the lungs. Chest radiography appearances vary from confluent irregular masses

### Expanded WHO case definition for AIDS surveillance

For the purposes of AIDS surveillance, an adult or adolescent (older than 12 years of age) is considered to have AIDS if a test for HIV antibody gives a positive result and one or more of the following conditions are present:

- 10% body weight loss or cachexia, with diarrhoea or fever, or both, intermittent or constant, for at least one month, not known to be caused by a condition unrelated to HIV infection
- Cryptococcal meningitis
- Pulmonary or extrapulmonary tuberculosis
- Kaposi's sarcoma
- Neurological impairment, which is sufficient to prevent independent daily activities, not known to be caused by a condition unrelated to HIV infection (for example, trauma or cerebrovascular accident)
- Candidiasis of the oesophagus (which may be presumptively diagnosed based on the presence of oral candidiasis accompanied by dysphagia)
- Clinically diagnosed life threatening or recurrent episodes of pneumonia, with or without aetiological confirmation
- Invasive cervical cancer

The boxes on WHO's case definition for AIDS surveillance are reproduced from Grant A, De Cock KM. HIV and AIDS in the developing world. In Adler M (ed) *ABC of AIDS*. 5th ed, London: BMJ Publishing Group, 2001

### Common AIDS defining diseases

#### Developed world

- Pneumocystis pneumonia
- Oesophageal candida
- Non-Hodgkin's lymphoma
- Tuberculosis (pulmonary and extra pulmonary)

#### Developing world

- Tuberculosis (pulmonary and extra pulmonary)
- HIV wasting syndrome
- Cerebral toxoplasmosis
- *Cryptococcus meningitis*



Kaposi's sarcoma

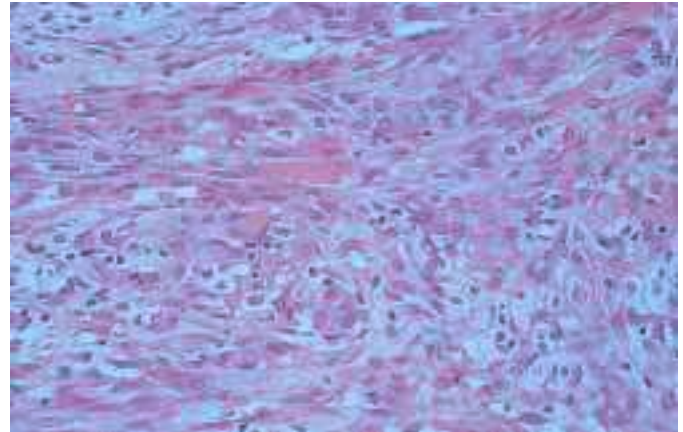


## ABC of Sexually Transmitted Infections

to interstitial nodularity. Computed tomography of the thorax may be useful in differential diagnosis. At bronchoscopy, endobronchial lesions may be seen. Kaposi's sarcoma consists of spindle shaped cells arranged in nodules and broad bands that contain vascular slits filled with extravasated erythrocytes.

The diagnosis of Kaposi's sarcoma in very early skin lesions may be extremely difficult because little more may be seen than a few irregular dilated vascular channels in the mid dermis and a mild inflammatory cell infiltrate.

Kaposi's sarcoma associated herpes virus (KSHV or human herpes virus 8) has been identified in nearly all Kaposi's sarcoma lesions and, when detected in blood, predicts the later development of Kaposi's sarcoma. Patient populations that have the highest risk of developing Kaposi's sarcoma (homosexual and bisexual men and Africans) have a high prevalence of antibodies to KSHV, and this correlates with the number of sexual partners and some past sexually transmitted infections (STIs) in homosexual men. Epidemiological evidence is supportive of sexual transmission and a causal role for KSHV in the pathogenesis of Kaposi's sarcoma. The mechanism for this is probably an interaction between KSHV replication, HIV proteins, inflammatory cytokines, and immune deficiency, which leads to a microenvironment that promotes the development of Kaposi's sarcoma.



Spindle cell proliferation of nodular Kaposi's sarcoma

### Non-Hodgkin's lymphoma

Extranodal disease is common and affects the central nervous system, bone marrow, and gastrointestinal tract. A diagnosis of non-Hodgkin's lymphoma should also be considered in patients with weight loss, constitutional symptoms, and anaemia. The tumours originate from B cells, are of high or intermediate grade, and generally have an aggressive clinical course. More than 50% of AIDS related lymphomas have been associated with the Epstein-Barr virus (EBV) or KSHV infection (or both). Although the incidence of AIDS related lymphoma has fallen as a result of HAART, it accounts for an increased proportion of the cause of AIDS related deaths. Non-Hodgkin's lymphoma unfortunately is difficult to treat and generally responds poorly to cytotoxic chemotherapy.

## Opportunistic infections

The organisms responsible for the opportunistic infections that occur in patients with AIDS are unusual pathogens. Most infections are caused by reactivation of latent organisms in the host or, in some cases, ubiquitous organisms to which we are continually exposed. The infections are frequently difficult to diagnose because conventional serological tests are unhelpful. Treatment often suppresses rather than eradicates the organisms. Therefore, without effective antiretroviral therapy, relapses are common. With effective antiretroviral therapy, the incidence of recurrent or new opportunistic infection falls dramatically.

Three main organ systems are affected: the respiratory system, the gastrointestinal tract, and the central nervous system. In addition, patients may present with a history of night sweats, chronic ill health, fevers, or weight loss.

## Pulmonary complications

*Pneumocystis jirovecii* (previously *carinii*) pneumonia is one of the most common life threatening opportunistic infections in patients who progress from chronic HIV infection to AIDS. The presentation is subacute, and malaise, fatigue, weight loss, and shortness of breath often develop over several weeks. Typical retrosternal or subcostal chest discomfort associated with



Extranodal lymphoma in the neck

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### Other neoplasms

- The incidence of cervical intraepithelial neoplasm and cancer is increased in HIV positive women
  - Similarly, squamous intraepithelial lesions and cancer of the anus are increased in HIV infected men and women
  - Both cervical intraepithelial neoplasia and squamous intraepithelial lesions are associated with human papillomavirus infections
  - An increased incidence of other cancers has been observed including Hodgkin's lymphoma and skin cancers
-

increasing shortness of breath, a dry cough, and fever finally causes the patient to seek help. The chest radiograph at presentation may be normal or show bilateral fine infiltrates, which are typically perihilar. The arterial oxygen tension is usually depressed and the carbon monoxide transfer factor, when available, is low and may be the earliest detectable abnormality. The diagnosis is confirmed by cytological examination of induced sputum or by fibre optic bronchoscopy and bronchial lavage. Transbronchial biopsy is now performed rarely. Bronchoscopy can exclude other causes of pneumonia or coexistent infection such as cytomegalovirus, mycobacteria, and fungi.

Pyogenic bacterial causes of pneumonia should always be considered, particularly as its presentation may be atypical. The radiological appearances may include diffuse infiltrates as well as the more typical focal or lobar patterns. Another cause of diffuse abnormality is lymphocytic interstitial pneumonitis, more common in children than adults with AIDS.

Infection with *Mycobacterium tuberculosis* may also occur and, since 1993, constitutes a diagnosis of AIDS. Among Africans who present with AIDS, it is the most common opportunistic infection and may present as pulmonary or extrapulmonary disease. In patients with advanced immunodeficiency, the presentation of pulmonary tuberculosis may be atypical and should be considered in all patients with respiratory symptoms. Multi drug resistant tuberculosis occurs. Atypical mycobacteria infection may occur but usually complicates severe immune depression of advanced AIDS.

## Gastrointestinal and hepatic complications

Oral and oesophageal candidiasis is the most common cause of dysphagia or retrosternal discomfort. Oral candidiasis alone does not fulfil the criteria for AIDS. Oesophageal infection is best shown by culture or biopsy at endoscopy, although plaques of *Candida albicans* often can be seen during a barium swallow. Ulceration may be focal or diffuse. Cytomegalovirus and herpes simplex virus may both cause a similar pattern of ulceration in the oesophagus (and also may affect the stomach and duodenum). Histopathology is needed to confirm the diagnosis.

Diarrhoea is a common symptom of patients with chronic HIV infection, with or without other manifestations of AIDS. In the majority of cases, a pathogen is found, although an enteropathy with malabsorption has been described as being secondary to HIV infection.

Cryptosporidium is a coccidian protozoal parasite and one of the most common pathogens isolated from AIDS patients who have diarrhoea. It is also the most common of the protozoal causes of diarrhoea, which also include *Isospora belli* and microsporidia. In immunocompetent human hosts, cryptosporidium produces a transient diarrhoeal illness. In people infected with HIV, it can cause transient, intermittent, or persistent diarrhoea ranging from loose stools to watery diarrhoea, colic, and severe fluid and electrolyte loss. Oocysts can be found in stools. If direct smears of unconcentrated faecal samples stained with iodine or modified acid fast stains fail to show the oocysts, the samples should be concentrated. The diagnosis should not be discounted without examining multiple specimens.

Microsporidia, small obligate intracellular protozoa, have been identified as a cause of diarrhoea in patients with AIDS where no other pathogen had previously been found.

### Effect on respiratory system—typical results from bronchoscopy series

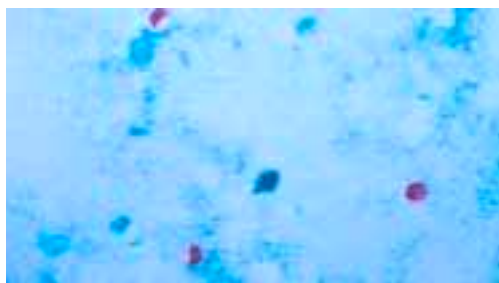
Condition	Percentage
<i>Pneumocystis jiroveci</i> pneumonia	70
Cytomegalovirus	15
Kaposi's sarcoma	5
Bacterial infection (pneumococcal, caused by <i>Haemophilus influenzae</i> or mycobacterial atypical or caused by <i>Mycobacterium tuberculosis</i> )	5
Miscellaneous	5



Chest radiograph of patient with typical appearances of *P jiroveci* pneumonia

### Gastrointestinal complications of AIDS

Complications	Causes
Retrosternal discomfort and dysphagia	Candidiasis Cytomegalovirus Herpes simplex virus
Diarrhoea, weight loss, and malabsorption	Unknown—enteropathy Cryptosporidiosis, <i>Isospora belli</i> , and microsporidial infection Cytomegalovirus and herpes simplex virus Mycobacteria Enteric bacteria—salmonella, campylobacter Neoplasia
Hepatitis and cholestasis	Mycobacteria Cytomegalovirus Drugs <i>Cryptosporidium</i>
Perianal ulceration	Herpes simplex virus ? Cytomegalovirus
Neoplasia and miscellaneous	Kaposi's sarcoma Lymphoma Hairy leukoplakia Recalcitrant anorectal warts ? Squamous oral or anal carcinoma (or both)



Cysts of *cryptosporidium* (modified Ziehl-Neelsen stain)



Severe mucocutaneous herpes simplex virus infection

Cytomegalovirus and herpes simplex virus can cause focal or diffuse ulceration of the gut, from the mouth to the anus. Herpes simplex virus most commonly causes mucocutaneous lesions at the upper and the lower ends of the gastrointestinal tract, whereas cytomegalovirus may mimic inflammatory bowel disease.

Atypical mycobacteria of the avium intracellulare complex are ubiquitous organisms that have little virulence for the immunocompetent host. Disseminated infection of several organs including the gastrointestinal tract occurs in patients with AIDS and may be associated with fever, weight loss, diarrhoea, and malabsorption. Diagnosis of disseminated infection is usually made on culture of blood or bone marrow biopsy. *Mycobacterium tuberculosis* infection of the bowel does occur but is less common. *Campylobacter* and *Salmonella* species infections may cause diarrhoea, but the latter more commonly presents as a fever of unknown origin with bacteraemia.

Hepatitis in patients with AIDS may present as fever, abdominal pain, and hepatomegaly, and liver function test results, particularly raised alkaline phosphatase activity, may be abnormal. If ultrasonography does not show dilated bile ducts, needle biopsy may show granulomatous hepatitis, usually caused by atypical mycobacteria rather than *M tuberculosis*. The herpes viruses also occasionally may cause hepatitis as part of a disseminated infection. Clinically the most common causes of hepatitis are drugs or coinfection with hepatitis B or C, which occurs most often among homosexual and bisexual men and injecting drug users than other patient populations.

Acalculous cholecystitis and cholangitis show an endoscopic retrograde cholangiographic picture similar to that of primary sclerosing cholangitis, with strictures and dilatation of the biliary tree. *Cryptosporidium* and cytomegalovirus have been shown or isolated and are implicated as a cause of this syndrome.



Dilated common bile duct with stricture at lower end and irregularities of extrahepatic and intrahepatic ducts

## Neurological complications

Chronic HIV infection is associated with several syndromes that affect the nervous system, in addition to the transient meningoencephalitis, myelopathy, and peripheral neuropathy of acute infection. These neurological diseases are believed to be caused by the direct or indirect effects of HIV and not to opportunistic infection. AIDS related dementia, also referred to as "HIV associated motor cognitive complex," has been estimated to occur in 10-40% of patients with symptomatic disease before the era of HAART. At necropsy, up to 90% of patients dying of AIDS have chronic subcortical encephalitis characterised by infected macrophages and microglial cells that fuse to form multinucleate giant cells. There is also patchy demyelination and astrogliosis.

The clinical features are characterised by cognitive and behavioural changes that include memory loss, apathy, and impaired concentration and attention. Neurological examination may show hyperreflexia, hypertonia, and frontal release signs. Computed tomography or magnetic resonance imaging often show cerebral atrophy and non-specific changes in the white matter. The findings in cerebrospinal fluid are

### Rough incidence of conditions in patients with neurological complications

Site of infection	Percentage
<b>Central nervous system</b>	
<i>Viral infections</i>	
AIDS related dementia	16
HIV related meningitis	13
Cytomegalovirus retinitis	5
Cytomegalovirus encephalitis	2
Progressive multifocal leukoencephalopathy	0.5
Vacuolar myelopathy	4*
<i>Intracranial mass lesions</i>	
Cerebral toxoplasmosis	14
Primary central nervous system lymphoma	4
Undefined mass lesions	3
Lymphoma	1
<b>Peripheral nervous system</b>	
Sensory neuropathy	16
Inflammatory demyelinating neuropathy	6
Cranial neuropathy	2
Multiple mononeuropathies	1
Polyradiculopathy	2
<b>Miscellaneous</b>	
Cryptococcal meningitis	6
Neurosyphilis	0.5
Metabolic encephalopathy	3
Cerebrovascular accident	0.5

\*may be as high as 20% at necropsy

non-specific. Opportunistic infections, intracranial mass lesions, metabolic encephalopathy, and neurosyphilis should be excluded.

HIV infection is also implicated in vacuolar myelopathy that affects primarily the posterior and lateral spinal cord, meningitis, and the following neuropathies: axonal sensory, chronic inflammatory demyelinating, and mononeuropathies. Cytomegalovirus infection may produce a polyradiculopathy.

The nervous system also is affected by opportunistic infection and tumours. Cerebral toxoplasmosis is the most common cause of intracranial mass lesions and usually presents with focal symptoms and signs. Cytomegalovirus commonly causes a retinitis and presents with blurring or partial loss of vision, or both. It may eventually lead to blindness.

## Treatment

### Antiretroviral therapy

In the developed world, combined antiretroviral therapies have led to dramatic falls in the incidence of new AIDS cases and AIDS associated deaths. The biological rationale for achieving and maintaining a clinical response to treatment has been established. Sustained inhibition of viral replication results in reconstitution of the immune system in most patients, substantially reducing the risk of clinical disease progression and death. Reservoirs of HIV in latently infected resting T lymphocytes and other long lived cell populations make it unlikely, however, that HIV can be eradicated by antiretroviral therapy alone.

Three main classes of antiretroviral drugs currently are licensed for inclusion in treatment regimens. The nucleoside analogues and a non-nucleoside agent inhibit the viral reverse transcriptase enzyme that produces a DNA copy from the single strand of viral RNA. The protease inhibitors inhibit post-translational processing of viral proteins. Current standard regimens combine two nucleoside reverse transcriptase inhibitors with either one non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor. Various combinations are recommended in national guidelines and the choice of therapy for an individual patient depends on the drug toxicity profile, pill burden and dosing schedule, likelihood of adherence to a particular regimen, and drug interactions. Large randomised clinical trials are ongoing to evaluate whether starting with a NNRTI or protease inhibitor containing regimen is associated with a better treatment outcome in the long term.

Where possible, the objective of antiretroviral therapy is to reduce and sustain plasma viral load concentrations to below what can be detected by recurrent ultrasensitive viral load assays (< 50 copies/ml). Failure to suppress a viral load to this level of treatment is associated with increased risk of subsequent viral load rebound and the emergence of viral genotypic mutations associated with reduced drug susceptibility. Even in those patients with advanced disease who start antiretroviral therapy at very low CD4 counts, sustained inhibition of viral replication does result in substantial immune reconstitution and a decreased incidence of AIDS defining illnesses and death. It has been estimated from cohort studies that the incidence of new AIDS illnesses or death in patients with a CD4 count persistently below  $50 \times 10^6/l$  is 55-70 events per 100 person years, whereas in those patients whose CD4 count rises to above  $200 \times 10^6/l$ , this event rate falls to between three and six events per 100 person years.

### Recommendations for starting antiretroviral therapy in adults

Disease stage	BHIVA	USDHHS
Symptomatic	Treat	Treat
Asymptomatic $CD4 < 200 \times 10^6/l$	Treat	Treat
CD4 count $200-350 \times 10^6/l$	Consider treatment depending upon viral load, rate of CD4 count decline, symptoms, and patient wishes	Treatment should generally be offered
$CD4 > 350 \times 10^6/l$	Defer	Defer or consider treatment if high viral load

BHIVA, British HIV Association Guidelines, March 2001; USDHHA, United States Department of Health and Human Services, February 2001. Reproduced from Weller I, Williams I. Treatment of infections and antiviral therapy. In Adler M (ed). *ABC of AIDS*. 5th ed. London: BMJ Publishing Group, 2001

### Drug toxicities

Drug	Toxicity
<b>NRTIs</b>	
Class associated	Lactic acidosis Hepatic steatosis Lipodystrophy (peripheral fat wasting)
Drug specific	
Zidovudine	Bone marrow suppression, nausea, vomiting, myopathy
Stavudine Zalcitabine	Peripheral neuropathy, hepatitis Peripheral neuropathy, mouth ulcers
Didanosine	Pancreatitis, dry mouth, peripheral neuropathy
Lamivudine Abacavir	Few side effects Hypersensitivity reaction, nausea
<b>NNRTIs</b>	
Nevirapine	Rash, hepatitis, Stevens-Johnson syndrome
Efavirenz	Rash, dysphoria, mood changes, vivid dreams, hypercholesterolaemia, hepatitis
<b>Protease inhibitors</b>	
Class specific	Lipodystrophy (fat wasting or accumulation), hyperlipidaemia, diabetes mellitus
Drug specific	
Nelfinavir Saquinavir Indinavir	Diarrhoea, rash Few side effects Hyperbilirubinaemia, nephrolithiasis, nail changes, dry skin
Ritonavir	Perioral dysaesthesia, flushing, hepatitis, diarrhoea, nausea, vomiting
Amprenavir Lopinavir	Rash, nausea, vomiting Diarrhoea

Reproduced from Weller I, Williams I. Treatment of infections and antiviral therapy. In Adler M (ed). *ABC of AIDS*. 5th ed. London: BMJ Publishing Group, 2001

## ABC of Sexually Transmitted Infections

Although the clinical effectiveness of antiretroviral therapy has improved, only about 70% of clinic patients sustain their plasma viral loads to  $< 50$  copies/ml at one year. An important factor associated with treatment success is adherence. Patients who are able to tolerate and adhere to their treatment regimen successfully are more likely to achieve and sustain suppression of plasma viral load than those who do not. Adherence is a factor in the choice of regimen and an important aspect of clinical care in patients on long term therapy.

Randomised clinical studies have not established when to initiate therapy. Recommendations are based on the knowledge of the risk of clinical disease progression (as determined by CD4 count and plasma viral load) and the likelihood of clinical benefit of therapy versus the likelihood of drug toxicity in the short term. Clinical practice across Europe and North America varies, but most clinicians will consider initiating therapy at some point between a CD4 count of  $200-350 \times 10^6/l$  and in all patients who have symptomatic disease. Patients on therapy should have CD4 count and plasma viral load concentrations monitored at regular intervals. On effective therapy, the plasma viral load falls rapidly, as viral replication is inhibited. By four weeks, a fall of greater than 1 log and by three to six months a fall to less than 50 copies per ml should be expected.

Problems with the current therapies include drug resistance and long term drug toxicity. Mutations associated with drug resistance will develop in patients who experience virological failure on therapy. For some drugs, the emergence of a single point mutation confers a very high decrease in susceptibility, whereas for other drugs the decrease in susceptibility is much lower and multiple mutations may be needed to confer high-level drug resistance. Cross resistance between drugs can also occur. Genotypic resistance testing is useful in guiding the choice of second and third line treatment regimens. Drug resistant viruses can be transmitted, and various recent studies in different parts of the developed world have shown that 10–15% of patients who present with primary HIV infection have genotypic mutations associated with drug resistance.

### Opportunistic infections and tumours

Advances in managing and preventing opportunistic infections have occurred and contributed substantially to the improvement and survival of patients with symptomatic disease that occurred before 1996. Both primary and secondary prophylaxis of opportunistic infections remain important in patients with severe immunodeficiency. However, the most effective strategy to prevent new AIDS defining illnesses or relapse of opportunistic infections is treatment with antiretroviral therapy, which results in the sustained control of virus replication and an increase in CD4 count. Both primary and secondary prophylaxis can be discontinued once the CD4 count rises ( $> 200 \times 10^6/l$ ) without risk of recurrence.

### Primary care

The care of patients with HIV infection has, in the most part, been the responsibility of specialist centres, which has reflected the complexity of the disease management, including therapy. Primary care physicians, however, can play an important role in certain areas. The first is diagnosis in people unaware of their HIV infection. Many patients first present to their doctor with the first symptoms of HIV associated immune deficiency. Awareness by the doctor of the signs and symptoms that might indicate HIV infection can lead to earlier diagnosis and referral for therapy. A substantial proportion of newly diagnosed patients continue to present late with an AIDS defining illness, and this is associated with increased mortality.

**Drug toxicity is important in determining tolerability and adherence to a regimen. Problems include peripheral neuropathy, cytopenia, pancreatitis, hepatitis, rash, hyperlipidaemia, and lipodystrophy. Peripheral lipoatrophy and visceral adiposity are features of the lipodystrophy syndrome. Although related to therapy, the pathogenic mechanisms remain uncertain**

**New formulations of current drugs and new agents are being developed. In addition to new reverse transcriptase and protease inhibitors, new drugs that act at different sites in the viral replication cycle are being developed. These include HIV entry inhibitors that affect CD4 and coreceptor attachment and fusion. Immunotherapeutic approaches are also being assessed, including the use of cytokines such as interleukin 2**

### Opportunistic infections: recommendations for initiation of primary prophylaxis

Opportunistic infection	Recommendations
<i>P. jiroveci</i> pneumonia	CD4 count $< 200 \times 10^6/l$
Cerebral toxoplasmosis	CD4 count $< 100 \times 10^6/l$ and positive immunoglobulin toxoplasma serology
<i>Mycobacterium avium</i> complex	CD4 count $< 50 \times 10^6/l$
Cytomegalovirus disease	Under evaluation: may consider if CD4 $< 50 \times 10^6/l$ and positive cytomegalovirus viraemia
Tuberculosis	If recent close contact of smear positive index patient and no evidence of active clinical disease. National guidelines for use of tuberculin skin testing for screening varies

Reproduced from Weller I, Williams I. Treatment of infections and antiviral therapy. In Adler M (ed). *ABC of AIDS*. 5th ed. London: BMJ Publishing Group, 2001

**Opportunistic infections: treatment recommendations**

Infection	Drug	Duration	Side effects	Comments
Pneumocystis pneumonia	Cotrimoxazole (trimethoprim component 15-20 mg/kg/day) orally or intravenously	21 days	Nausea, fever, rash, bone marrow suppression	80% of patients will respond to treatment Secondary prophylaxis with low dose cotrimoxazole, dapsone, or nebulised pentamidine is required until CD4 count increases to $>200 \times 10^6/l$ on antiretroviral therapy
	or pentamidine isetionate 4 mg/kg/day as slow intravenous infusion	21 days	Hypotension, hypoglycaemia, renal failure, hepatitis, bone marrow suppression	
	or clindamycin 600 mg six hourly orally or intravenously plus primaquine 15 mg/daily orally	21 days	Nausea, diarrhoea, rash, hepatitis  Nausea, methaemoglobinaemia, haemolytic anaemia, leucopenia	
Toxoplasmosis	Pyrimethamine 50 mg/day orally and either Sulphadiazine 4-6 g/day orally or intravenously or clindamycin 600 mg four times a day orally or intravenously	6 weeks	Rash, nausea, bone marrow suppression	Doses usually halved during maintenance Treatment is continued as secondary prophylaxis until CD4 count increases to $>200 \times 10^6/l$ on antiretroviral therapy
Cryptosporidiosis	Paromomycin 600 mg four times a day orally	28 days	Epigastric pain, dysphagia	Although observational studies report clinical improvement, paromomycin is an unlicensed drug Improving CD4 count with antiretroviral therapy can result in resolution of symptoms and infection
Herpes simplex infection	Aciclovir 200 mg five times/day orally or 5-10 mg/kg eight hourly intravenously	10-14 days		Suppressive treatment with aciclovir 400 mg twice daily often required
Cytomegalovirus	Ganciclovir 5 mg/kg twice daily intravenously or valganciclovir 200 mg twice daily orally	21 days	Anaemia, neutropenia	Marrow suppression potentiated with zidovudine Secondary prophylaxis with lower doses is required until CD4 count increases to $>100 \times 10^6/l$ on antiretroviral therapy
	or foscarnet 90 mg/kg twice daily intravenously	21 days	Nephrotoxicity, hypocalcaemia, headache	
	or cidofovir 5 mg/kg weekly intravenously*†	14 days	Nephrotoxicity, hypocalcaemia	
Candidiasis local treatment	Nystatin oral suspension or pastilles, miconazole oral gel, or amphotericin lozenges	As required		Relapse common, many patients with persistent severe immune deficiency require systemic treatment
Candidiasis systemic treatment	Fluconazole 50-200 mg/day	7-14 days	Hepatitis	Relapse common on cessation of treatment Relapse common on cessation of treatment
	or Itraconazole	7-14 days	Hepatitis	
Cryptococcosis	Amphotericin B 0.7-1 mg/kg/day with or without flucytosine 75-100 mg/kg/day in four divided doses	6 weeks	Nausea, vomiting, rash, bone marrow suppression, renal damage, hypocalcaemia	Liposomal preparations of amphotericin associated with reduced risk of nephrotoxicity Secondary prophylaxis with fluconazole 200-400 mg/day is required until CD4 count increases to $>200 \times 10^6/l$ on antiretroviral therapy
	or fluconazole 400-800 mg/day	6 weeks	Nausea, hepatitis	

\*Dose titrated to creatinine clearance

†Pre-dosing and post-dosing with probenecid limits risk of nephrotoxicity

## ABC of Sexually Transmitted Infections

Symptoms and signs suggestive of immune deficiency should prompt enquiry of previous high risk behaviour and possible exposure to HIV, particularly in those patient populations associated with higher prevalence.

Primary care is also important in the long term care of a patient, particularly the management of psychosocial and mental health problems, drug side effects, pain control, and palliative care—issues that are common to the treatment of other chronic and disabling conditions. For this reason and as the ongoing care of other general medical problems in primary care will be better managed if the doctor is aware of the HIV status of the patient, it is important that all patients are registered with a doctor.

In addition, doctors can play an important role in prevention, by promoting safer sex behaviour and by improving diagnosis and treatment of STIs in primary care.

### Therapy in the developing world

The challenge to provide effective therapy in the developing world is immense. In 2001, the United Nations declared that treatment and care services, including access to antiretroviral drugs, is an essential element of the response to the global HIV and AIDS epidemic and described the features of comprehensive care that need to be developed. Several major problems exist in the developing world. These include the unavailability of HIV diagnostic tests such that the majority of people with HIV remain unaware of their status, the cost of antiretroviral drugs, which, despite reductions, still greatly exceed the annual per capita health expenditures of most developing countries, the fact that healthcare systems are ill equipped to deliver effective care, and the widespread fear and stigma associated with HIV and AIDS.

Despite these problems, the provision of care and access to antiretroviral therapy is improving in many countries through both government and private industry initiatives. These include increased access to treatments of opportunistic infections and improved healthcare systems at a community level to support the provision of antiretroviral therapy. However, at every level, regional, governmental, and community multiple challenges remain.

In June 2002, the WHO produced guidelines for scaling up the antiretroviral therapy in resource limited settings.

- When to start therapy is based on clinical plus CD4 count or total lymphocyte criteria
- An assessment of viral load is not considered essential before therapy
- It is recommended that within each country's treatment programmes, therapy regimens should be standardised, with a single first line regimen and a limited number of second line regimens for large scale use
- Programmes should recognise that people who cannot tolerate or who fail standardised regimens should be referred for individualised care by specialist physicians
- Triple combination regimens are recommended, dual nucleoside analogue regimens are no longer reasoned to be acceptable
- Changing therapy because of treatment failure should be based on clinical and CD4 count criteria
- The absolute minimum tests required for a treatment programme is HIV serology and haemoglobin
- Basic recommended laboratory tests, largely to monitor for drug toxicity, include a white blood cell count, differential, serum alanine or aspartate aminotransferase, serum creatinine or blood urea (or both), serum glucose, and pregnancy tests. CD4 counts are considered desirable and viral load testing optional.

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### Symptoms and signs of symptomatic (non-AIDS) HIV disease

The presence of these features should prompt discussion of HIV testing in those unaware of their HIV status

- Oral hairy leucoplakia
  - Recurrent of multi-dermatomal herpes zoster
  - Unexplained weight loss, chronic diarrhoea, and night sweats
  - Recurrent or persistent oral candida
  - Unexplained persistent generalised lymphadenopathy
  - Chronic severe skin conditions, for example seborrhoeic fungal infections
  - Peripheral neuropathy
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### United Nations AIDS declaration (2001): features of comprehensive care for people living with HIV and AIDS

- Available, accessible voluntary counselling and testing services
  - Prevention and treatment of HIV related illnesses
  - Provision of antiretrovirals
  - Prevention and treatment of tuberculosis and other infections
  - Prevention and treatment of STIs
  - Prevention of further HIV transmission
  - Palliative care
  - Family planning
  - Good nutrition
  - Social, spiritual, psychological, and peer support
  - Respect for human rights
  - Reduction of the stigma associated with HIV and AIDS
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### Antiretroviral therapy in a resource limited setting: WHO recommendations, June 2002

#### When to start therapy

- WHO stage IV of HIV disease (clinical AIDS), regardless of CD4 count
- WHO stages I, II, or III of HIV disease, with a CD4 count below 200/mm<sup>3</sup>
- WHO stages II or III of HIV disease with total lymphocyte count below 1200/mm<sup>3</sup>

#### Recommended first line regimens

- Zidovudine and lamivudine plus nevirapine or efavirenz
- Zidovudine and lamivudine plus abacavir
- Zidovudine and lamivudine plus nelfinavir or low dose ritonavir boosted protease inhibitor

Other nucleoside analogue components can be substituted depending on country specific preferences

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### Prevention and control

As no cure or vaccine is currently available, our main weapon is prevention and control. An “information vaccine” is required. In any epidemic an accurate appreciation of the size of the problem and how it is changing is essential. With HIV infection this can be achieved by counting the number of patients with AIDS and monitoring the prevalence of HIV antibodies in low-risk and high-risk populations.

Of fundamental importance is good and accurate health education for those at low risk and those at high risk. People who are known to be infected or may have been exposed are advised not to donate blood, organs, or semen, to modify their sexual behaviour, and to avoid behaviour that is particularly likely to transmit the virus. The screening of blood donors for HIV antibodies and the heat treatment of blood products have virtually eliminated the risk to recipients. The treatment and control of STIs is also important, as they are cofactors in transmission. Reductions in mother to child transmission rates have been achieved through the use of antiretroviral therapy and in developed countries the rate has fallen to only 1-2%.

### Prevention and control

- Surveillance
- Counselling and health education
- Screening of people and donated blood
- Heat treatment of blood products
- Strategies to reduce high risk behaviour in targeted populations
- Antiretroviral therapy to reduce mother to child transmission
- Protection of healthcare staff
- Treatment and control of STIs

**The evidence for the efficacy of post-exposure prophylaxis after either occupational or sexual exposure to HIV is limited. However, in clinical practice it is common to consider post-exposure prophylaxis after considerable exposure to HIV, usually by a needle stick injury. It is recommended that combination antiretroviral therapy be started as soon after the exposure incident as possible, preferably within 24 hours, for duration of four weeks**

### Proposed WHO staging system for HIV infection and disease

#### Clinical staging

Patients with HIV infection who are  $\geq 13$  years are clinically staged on the basis of the presence of the clinical condition or performance score, belonging to the highest level.

- Clinical stage 1: asymptomatic or persistent generalised lymphadenopathy, performance scale 1 (asymptomatic, normal activity)
- Clinical stage 2: weight loss  $< 10\%$  of body weight, minor mucocutaneous manifestations, varicella zoster within the last five years, recurrent upper respiratory tract infections (bacterial sinusitis), performance scale 2 (symptomatic but normal activity)
- Clinical stage 3: weight loss  $> 10\%$  of body weight, unexplained chronic diarrhoea for more than one month, unexplained chronic fever for more than one month, oral candidiasis, oral hairy leukoplakia, pulmonary tuberculosis within the past year, severe bacterial infections, performance scale 3 (bedridden  $< 50\%$  of day during the last month)
- Clinical stage 4: most other CDC AIDS defining diseases (but not pulmonary tuberculosis), performance scale 4 (bedridden  $> 50\%$  of day during the last month)

### Proposed WHO clinical and laboratory classification for HIV infection and disease

	Laboratory axis			Clinical axis		
	Lymphocytes ( $\times 10^6/l$ )	or CD4 ( $\times 10^6/l$ )	1 Asymptomatic	2 Early	3 Intermediate	4 Late
A	$> 2000$	$> 500$	1A	2A	3A	4A
B	1000-2000	200-500	1B	2B	3B	4B
C	$< 1000$	$< 200$	1C	2C	3C	4C

The tables above are reproduced from Grant A, De Cock KM. HIV and AIDS in the developing world. In Adler M (ed) *ABC of AIDS*. 5th ed, London: BMJ Publishing Group, 2001



# 17 Laboratory diagnosis of sexually transmitted infections

Beryl West

Laboratory diagnosis plays an important part in sexually transmitted infection (STI) control, both in treatment decisions for individual patients and in aetiology studies for designing control programmes. However, constraints that limit what laboratory services are available and practical in many settings exist in terms of costs, available expertise, and support systems. Some of the methods available for diagnosis, the equipment and expertise needed to perform the tests, and the suitability for use in clinics or specialised laboratories are discussed. The quality of samples and testing methods, bedside/clinic rapid diagnostic tests are also covered.

## Gonorrhoea

The causative organism is *Neisseria gonorrhoeae* (see Chapter 5). A number of different tests are available for laboratory diagnosis, identification, and classification of *N gonorrhoeae*, ranging from a simple Gram stain to complicated molecular techniques. The method used depends on several logistical factors, such as equipment, technical expertise and space available, support services, availability of supplies, and the intended use of the results, as well as financial constraints.

Certain factors need to be taken into consideration when choosing testing methods in different healthcare settings. Thus, a simple Gram staining method could be established at

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### Some methods used in the diagnosis of *N gonorrhoeae*

#### Specimen collection

- Use sterile swabs or loops, prepare smear at bedside or clinic, and inoculate directly onto culture media or put immediately in a non-nutritive transport media, such as Stuart or Amies media

#### Gram stain

- Microscopy—detects leucocytes and intracellular Gram negative diplococci

#### Culture (direct or inoculated from swabs in transport media)

- Incubation in 5% carbon dioxide atmosphere—use selective media (such as modified Thayer Martin media) for 24-48 hours at 35°C. Presumptive colonies are picked for identification

#### Presumptive identification

- Typical Gram negative diplococci seen on Gram stain, positive oxidase test

#### β lactamase testing

- Chromagenic cephalosporin—rub growth from five colonies onto rehydrated nitrocefin disc or emulsify in nitrocefin reagent on slide—a positive reaction (red colour) detects penicillin resistance

#### Antimicrobial susceptibility testing

- Minimum inhibition concentration testing or disc diffusion tests detect trends in resistance to antibiotics and plasmid carriage
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### Choosing appropriate diagnostic testing methods

Setting	Diagnostic tests	Equipment and consumables	Expertise required	Usefulness
Primary level health provision or general practice	Gram stain	Microscope, Gram stains	Smear interpretation	Diagnosis of gonorrhoea and non-gonococcal urethritis in men. Sensitivity and specificity in male urethral smears are 95% and 97%, respectively In females, cervical Gram films only detect 40-60% culture positive samples Rectal swabs are only useful if rectal mucosa is sampled through a proctoscope, this yields easily interpretable results Pharyngeal swabs are not useful as morphologically similar organisms are in the pharynx
Intermediate level health provision or district general hospital	Gram stain, culture, presumptive identification	Microscope, incubator, carbon dioxide jar, Gram stains, culture media, oxidase reagents	Smear interpretation, recognition and identification of <i>N gonorrhoeae</i> on culture plates	Culture yields the most accurate diagnosis of gonorrhoea from all sites Enables collection of isolates for further epidemiological studies and antimicrobial susceptibility
Central laboratory or reference laboratory or teaching hospital with laboratory attached	Gram stain, culture, identification strain typing, antimicrobial susceptibility testing, ligase chain reaction or polymerase chain reaction	Microbiology laboratory equipment and supplies, typing reagents, molecular biology systems, minimum inhibitory concentration testing systems	Trained microbiologist	Diagnosis, epidemiology, aetiology, susceptibility

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a primary healthcare setting with a minimum of equipment and staff training; however, the more advanced tests require a well equipped laboratory and trained staff.

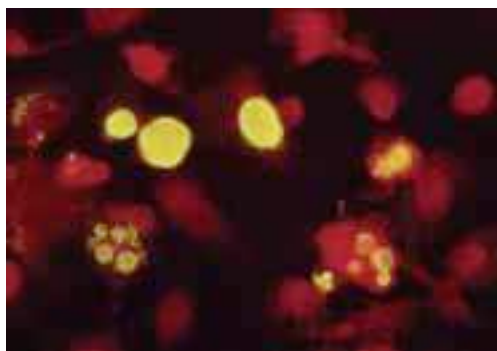
## Gram staining method

- Prepare smear by rolling the swab over the surface of a glass slide or inoculating from loop, dry, and fix by passing rapidly three times through a flame
- Flood the smear with crystal violet for one minute, rinse under tap
- Flood the slide with Lugol's iodine for one minute, rinse under the tap
- Decolorise with acetone-ethanol for 10-20 seconds until blue is removed from smear, rinse well with water
- Counter stain with safranin or fuchsin for one minute, rinse well, and gently blot dry
- Examine microscopically using  $\times 100$  objective
- *N gonorrhoeae* appear as Gram negative (red) diplococci often within polymorphonuclear leucocytes. Describe what is seen on the smear, types of cells, extracellular or intracellular bacteria, and count the numbers of leucocytes per high power field

## Chlamydia infections

The causative organism, *Chlamydia trachomatis*, has a unique growth cycle. The elementary body is the infectious form that is adapted to live in an extracellular environment and is the usual target of detection methods.

All diagnostic tests for *Chlamydia* require special equipment and technical expertise, which make them unsuitable for use in primary healthcare settings. Ocular staining could be carried out at intermediate level laboratories if expertise in reading slides is available. Fluorescence detection, enzyme linked immunosorbent assay (ELISA) techniques, and polymerase chain reaction (PCR) and ligase chain reaction (LCR) methods must be used in specialised laboratories equipped with fluorescence microscopy, ELISA readers, washers, and molecular biology systems.



Green and yellow fluorescent stained inclusions of *C trachomatis* in tissue culture cells

## Vaginal discharge infections

The most common causes of vaginal discharge are *Trichomonas vaginalis*, *Candida*, and bacterial vaginosis. *Trichomonas* and *Candida* can be detected with wet preparation microscopy at the clinic or by culture methods in a laboratory (see Chapter 7). Bacterial vaginosis can be determined with clinical criteria, Amsel's score, or by using a Gram staining method, such as Nugent's score.

A positive Amsel's score is based on the presence of three of four of the following

- Characteristic homogeneous, white-grey, adherent discharge
- Vaginal pH  $> 4.5$



Colonies of a pure culture of *N gonorrhoeae* growing on a modified Thayer Martin plate

## Detection of *Chlamydia trachomatis*

### Specimen collection

- Preferable to use cervical or urethral specimens collected by swab or loop; however, first void urine then self administered vaginal swabs or tampons can be used with some detection techniques.
- Use appropriate swabs, non-toxic for tissue culture and Dacron for nucleic acid detection methods. Cytobrush samples also give good yields.
- Put swabs immediately in appropriate transport media. Store cold before transport to the laboratory

### Direct microscopy

- Giemsa staining, useful for eye infections but lacks sensitivity for genital specimens

### Culture

- Tissue culture with McCoy cells; this used to be the most sensitive method but is time consuming and has now been superseded by nucleic acid detection in many laboratories

### Direct immunofluorescence

- Direct antibody staining with fluorescence labelled antibody, has 92% sensitivity, 97% specificity in symptomatic men, 79% sensitivity, and 98% specificity in women with intermediate prevalence

### Enzyme immunoassays

- ELISA techniques to detect *Chlamydia* lipopolysaccharide antigens. Sensitivity low: 50-80% depending upon population and test used. Specificity is good at around 95%

### Nucleic acid detection

- LCR and PCR kits are available. Good sensitivity and specificity: sensitivity ranges from 95% in male urine to 98% in female cervical swabs, and specificity around 99% for all samples

## Overview of vaginal discharge infections

### Specimen collection

- Vaginal swab, preferably from the wall of posterior fornix. Either do direct microscopy immediately or place swab in transport media, this must be read within two hours

### Wet preparation

- Microscopic examination for the presence of *T vaginalis*, *Candida*, and the presence and approximate percentage of clue cells

### Potassium hydroxide preparation

- Smell for typical amine smell of whiff test, microscopically examine for *Candida*

### pH

pH test with pH paper

### Gram stain

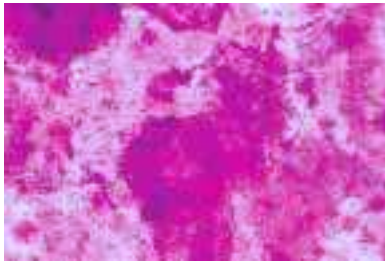
- Nugent's score for bacterial vaginosis

### *T vaginalis* or *candida* culture

- InPouch or Diamond media for *T vaginalis*, Sabouraud agar plates for *Candida*. Feinberg-Whittington media can be used for both *Candida* and *T vaginalis*

## ABC of Sexually Transmitted Infections

- Release of a fishy odour from vaginal fluid mixed with 10% potassium hydroxide solution (whiff test)
- >20% clue cells.



Gram stain vaginal smear showing bacterial vaginosis as detected by Nugent's score of 10

A positive Nugent's score is based on the types of bacteria present in a Gram stained vaginal smear and the numbers of Gram positive lactobacilli and the numbers of Gram negative or Gram variable coccobacilli are estimated per high power field.

- Predominance of lactobacilli—0-3 (negative)
- Mixed flora—4-6 (intermediate)
- Predominance of Gram negative coccobacilli—7-10 (positive for bacterial vaginosis).

The sensitivity of a wet preparation for detecting *T vaginalis* is 36-60%, depending upon patients, and the sensitivity of cultural methods is 80-95%. A positive wet preparation has a high diagnostic value for *Candida*. However, a positive culture does not necessarily indicate a need to treat, because more than 20% of healthy women are carriers. Culture is useful if the wet preparation is negative and *Candida* is suspected clinically. Amsel's score has a sensitivity of around 78% for bacterial vaginosis compared with Nugent's score.

A wet preparation and Amsel's score give immediate and very useful results for managing vaginal discharge and can be incorporated at the primary healthcare level. Culture methods and the interpretation of Nugent's score need more facilities and expertise.

## Syphilis

Venereal syphilis is caused by the spirochaete *Treponema pallidum* and can be diagnosed directly from clinical lesions by dark ground microscopy. However, the use of dark ground microscopy is limited by the need for strict technical conditions and expertise to produce reliable results, which makes it difficult to use. Alternative methods to detect syphilis in genital lesions are the direct fluorescent antigen test or the newer DNA amplification tests, such as the polymerase chain reaction (PCR) method.

Traditionally, syphilis has been diagnosed by serological testing for antibodies (see Chapter 12).

- Swab ulcerated lesions—use Dacron swabs for nucleic acid detection methods
- Store cold before transport to the laboratory
- Take whole blood sample to collect serum for serology.

## Herpes

Genital herpes is most frequently caused by infection with herpes simplex virus type 2 (HSV-2) but can also be caused by HSV-1 (see Chapter 11). Genital HSV-1 acquired through orogenital contact is increasingly common in western Europe and North America. Recurrent genital herpes episodes occur more commonly in infections caused by HSV-2.

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### Wet preparation method

- Add one drop of saline to one end of a clean glass slide and one drop of 10% potassium hydroxide to the other end
  - Mix vaginal swab first in the saline and then in the potassium hydroxide drop to form an even suspension
  - Smell the potassium hydroxide drop to detect any fishy odour
  - Cover drops with cover slips
  - Examine saline drop first using  $\times 10$  objective to scan the slide and the  $\times 40$  objective to examine more closely. Look for *T vaginalis* and clue cells and note the presence of any other cells
  - *T vaginalis* is a pear shaped flagellate, 12-25  $\mu\text{m}$  long, with flagella attached to an undulating membrane that extends the length of its body; it is recognised by typical motility
  - Clue cells are squamous epithelial cells covered with many small coccobacillary organisms, which give a granular effect, with the edges of cells not clearly defined. In bacterial vaginosis, 20% of cells will be clue cells
  - Examine potassium hydroxide preparation in the same way, look for yeast cells. Yeasts are round to ovoid (4  $\mu\text{m}$ ) and show typical budding and presence of mycelia
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### Serological testing for syphilis

#### Non-treponemal tests

- Most common are rapid plasma reagin (RPR) and Venereal Disease Reference Laboratory (VRDL) tests—a positive result may indicate a current infection, recent past infection, or a biological false positive (1-3%). These can be quantitatively tested to give a known titre; false positives usually have a titre below 1:4. Confirm positives with a treponemal test

#### Specific treponemal tests

- Commonly used *Treponema pallidum* haemagglutination particle agglutination (TPHA), fluorescent antibody detection (FTA-Abs), or antibody detection immunoglobulin G and immunoglobulin M fluorescent immunoassays (EIA)—a positive result may indicate current infection or past infection

#### Diagnosis of "active syphilis"

- Screen serum with non-treponemal test and confirm with specific treponemal test or use a single enzyme immunoassay. Simple RPR testing can be done at primary healthcare settings and can be used for screening in STI and antenatal clinic populations. The more complex serological techniques need specialised equipment and are more suited for confirmatory testing in centralised laboratories
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### Methods for testing for herpes

#### Sample collection

- Swab lesion exudate where possible, use appropriate swabs, non-toxic for tissue culture and Dacron for nucleic acid detection methods. Put swabs immediately in appropriate transport media. Store cold before transporting to the laboratory
- Take whole blood sample to collect serum for serology

#### Methods for detection of herpes simplex virus type 2 (HSV-2) antigen in lesions or in asymptomatic carriers

- Viral isolation using tissue culture—use cells such as human diploid fibroblasts or Vero cell lines
- Direct detection of antigen with fluorescent labelled specific monoclonal antibody to HSV-2—this can be done using lesion exudate on a slide and examining with fluorescent microscopy
- Direct detection of antigen using an antigen detection ELISA, available as a kit—when compared with viral isolation in symptomatic patients sensitivity is 70-95% and specificity is 94-100%; however, sensitivity is low in asymptomatic patients
- Nucleic acid detection—several good polymerase chain reaction (PCR) methods are available

#### Serological antibody detection

- Can show present or past infection. A wide range of assays are commercially available, the most sensitive assays are enzyme immunoassay based on glycoproteins specific to HSV-2
-

Although mainly diagnosed on clinical grounds, laboratory diagnosis is important for differential diagnosis to exclude other genital ulcer diseases and in giving appropriate advice and counselling. However, the diagnostic methods are not suitable for use in primary or intermediate healthcare facilities and need to be carried out in specialised laboratories.

## Chancroid

Chancroid is an acute ulcerative STI caused by the bacteria *Haemophilus ducreyi*. Laboratory diagnosis is based on detection of the organism from lesions.

## Other STI organisms

Other organisms than those referred to here can be responsible for STI infections. These can depend upon geographical location, such as *Calymmatobacterium* or *Klebsiella granulomatis* the causative organism of granuloma inguinale (donovanosis). Hence, knowledge of local aetiologies is important when looking at what diagnostic tests to use.

Other organisms have more tenuous links to STIs and at present are not part of routine screening—for example, mycoplasma and ureaplasma. It is also important to note that it is not possible to identify a pathogen in all STI cases and these have to be treated symptomatically or syndromically.

## Rapid tests

A new generation of rapid bedside tests are now available for STI diagnosis that can be used in the clinic to aid diagnosis and treatment decisions. A large variety of such tests are on the market for measuring syphilis serology and *Chlamydia* and gonorrhoea antigens, and latex agglutination tests for *T vaginalis* and *Candida*. The efficiency of these tests varies widely between the types of test and manufacturer and reported sensitivity and specificities may be based on limited evaluations. If they are to be used, the rapid test must be chosen carefully with all available evaluation data.

At present, the most useful rapid screen in cases of genital discharge, particularly in women, is for gonorrhoea and *Chlamydia*. For this purpose, rapid testing technology is based on antigen detection, either with immunochromatographic detection or optical immunoassay.

Tests for *Chlamydia* are more advanced and several are available commercially, such as Clearview (Unipath, UK), Quickvue (Quidel, USA), and Chlamydia OIA (ThermoBioStar, USA). The most rapid tests for gonorrhoea are still in development but a few are available now, such as OIA Gonorrhoea (ThermobioStar USA) and NOW CC (Binax, USA).

The main disadvantages of rapid tests are that many are not properly validated, some are not as easy to read or as easy to perform as stated in the product literature, and they are relatively expensive. Availability and costs are a major hurdle to introducing syndromic management programmes in resource poor settings. At present, the World Health Organization's Rapid Diagnostics Evaluation Scheme for STIs is evaluating rapid tests for performance and operational characteristics that are appropriate to use in

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## Chancroid

### Sample collection

- Collect a swab from ulcer exudate, choose appropriate swab. Prepare smear and immediately directly inoculate culture plate or store in transport media

### Direct examination

- Preparation of Gram stained smears is possible at primary level, look for typical small Gram negative bacilli grouped in chains or "schools of fish." Typical slides are seen infrequently, however, and sensitivity is less than 50%

### Culture

- *Haemophilus ducreyi* requires enriched media and microaerophilic conditions for growth. Good laboratory conditions are needed to isolate and identify. Isolates can be used to determine antimicrobial susceptibility patterns

### Antigen detection

- Fluorescent labelled monoclonal antibodies, blot radioimmunoassay

### Nucleic acid detection

- Polymerase chain reaction methods are available
- 

All rapid tests give results within 20 minutes with a minimum of technical procedures and require little training and no equipment



Rapid test for syphilis

## ABC of Sexually Transmitted Infections

primary health care settings. This may result in the most promising rapid tests being made more widely available and at affordable rates.

### Quality control

A laboratory test is only as good as the specimen taken, the quality of the testing procedures, and the carefulness and expertise of the tester.

The photograph of the gram stain vaginal smear is courtesy of Dr Catherine Ison, Department of Infectious Diseases and Microbiology, Imperial College School of Medicine, London.

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#### Quality control

##### Quality of samples taken

- Adequate samples must be obtained, particularly when collecting cervical swabs for *Chlamydia*, which are intracellular. The correct swabs must be used, for example, Dacron for the PCR method

##### Quality of sample processing at bedside

- Label samples and process immediately in appropriate transport media or direct plate inoculation and Gram smear preparation. Do not make the Gram smear too thick

##### Quality of testing procedures

- Tests chosen have different specifications. The sensitivity and specificity will give an idea of the expected false positive and false negative rates

##### Expertise of tester

- Good training and standard operating procedures are needed to ensure tests run correctly and uniformly

##### Internal and external quality control measures

- Internal quality control can be practised with a second reader to repeat read a proportion of wet preparations and Gram stain smears. Culture methods have inbuilt quality control on media.
  - External quality control is only really appropriate for intermediate or reference laboratories. Schemes are available for microbiology and serology
-

# Appendix: male and female proformas for taking sexual histories

**MALE** (New patient/episode)

**PATIENT  
STICKER**

**DATE**                      **SEEN BY (print/stamp)**

**Presenting complaint**

Last sexual contact	M/F	Reg./Cas./Known and duration	Country	TYPE OF SEX				Condoms used?	Condom breaks/failure?
				Oral	Vaginal	Anal	Other		

Number of partners in last 3/12

Past history of STDs

Past medical history

Hepatitis A/B vaccination

Medication

Allergies

Recreational drugs (last 3/12)

Injecting drug use

Smoking

Alcohol

HIV TEST

Previous test

Blood donor

Risks

Male partners

HIV positive partner

From high prevalence area

High risk partner

Window period

Expectation of result

PN/support

Test today

**EXAMINATION**

**LN**

**Testes**

**Penis**

**Perianal area**

Tests (stick pathology form here)

Nursing notes

**Diagnosis/Management Plan**

**Health promotion**

Safer sex

Condoms

HIV

HAV/HBV vaccine

Contraception

**Partner notification**

Contact slips issued (number)

**Treatment**

Checked for drug interactions Yes/No

**Referral to HA**

Reason

**Advice/information**

**KC60 Diagnosis codes**

- 1.
- 2.
- 3.
- 4.

**Orientation**

**Source of referral**

**GP letter required**

**Follow-up: Attend..... Letter..... Phone.....**

Doctor/SpN signature .....

Male proforma May 2003

**FEMALE** (New patient/episode)

**PATIENT  
STICKER**

**DATE**                      **SEEN BY (print/stamp)**

**Presenting complaint**

Last sexual contact	M/F	Reg/Cas/ Known and duration	Country	TYPE OF SEX				Condoms used?	Condom breaks/failure?
				Oral	Vaginal	Anal	Other		

Number of partners in last 3/12		Allergies
Past history of STDs		Recreational drugs (last 3/12)
Past medical history		Injecting drug use
Medication		Smoking
Current contraception		Alcohol
LMP                      Cycle		Sex work
Pregnancies		HIV TEST
Last Cytology                      Where taken		Previous test
Result                      Ever abnormal		Blood donor
		Risks
	HIV positive partner	
	Bisexual partner	
	From high prevalence area	
	Other high risk partner	
	Window period	
	Expectation of result	
	PN/support	
	Test today	

**EXAMINATION**

**LN**

**Vulva**

**Vagina  
pH**

**Cervix**

**Bimanual**

**Tests (stick pathology form here)**

**Nursing notes**

<p><b>Diagnosis/Management Plan</b></p>	<p><b>Health promotion</b></p> <p>Safer sex</p> <p>Condoms</p> <p>HIV</p> <p>HBV vaccine</p> <p>Contraception (including need for EC today)</p>
---	---

<p><b>Treatment</b></p> <p>Checked for drug interactions Yes/No</p>	<p><b>Partner notification</b></p> <p>Contact slips issued (number)</p> <p>Referral to HA Reason</p>
---	--

<p><b>Advice/information</b></p> <p>Follow-up: Attend..... Letter..... Phone.....</p>	<p><b>KC60 Diagnosis codes</b></p> <p>1.</p> <p>2.</p> <p>3.</p> <p>4.</p>	<p><b>Orientation</b></p> <p>Source of referral</p> <p>GP letter required</p>
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Doctor/SpN signature .....

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