Surveillance of sexually transmitted infections in primary care

I Simms, A-K Hurtig, P A Rogers, G Hughes, K A Fenton

What do we need to do?

Surveillance of sexually transmitted infections (STI) provides information for public health action, a relation that was highlighted by the “National Strategy for Sexual Health and HIV” published recently by the Department of Health (England). Systematically collected, timely, accurate, detailed, representative STI surveillance data are needed to estimate the population burden of disease; monitor effectiveness of STI prevention; evaluate healthcare access; and assess determinants of transmission. England has one of the world’s most comprehensive STI surveillance systems based on data from genitourinary medicine (GUM) clinics (the KC60 return) and laboratory reports. Data are widely disseminated and used in strategic health planning at national and local levels. A weakness in English surveillance is that it does not provide the information needed to interpret changes in STI epidemiology. This is not unusual as there are similar weaknesses in surveillance systems in other countries, such as Sweden. Both the KC60 and laboratory report systems are being redeveloped: patient based data collection is being introduced in GUM; enhanced surveillance programmes have been developed for syphilis and gonorrhoea; and the laboratory report system is being expanded. Although improvements in coverage, availability, quality, timeliness, and representativeness are anticipated, lack of data from primary care remains. Substantial reservoirs of predominantly asymptomatic STIs, such as Chlamydia trachomatis, genital herpes simplex virus infection (HSV), human papillomavirus infection, and pelvic inflammatory disease (PID) are known to be treated in primary care settings, including general practice and family planning.

Developments proposed in the national strategy suggest that STI diagnosis and management will be increasingly focused on primary care. The systematic collection of timely, representative data from primary care is needed if we are to address future prevention needs, an emerging challenge that requires novel approaches to surveillance. Here, we discuss a new method for estimating STI prevalence in primary care within the context of the available surveillance data.

AVAILABLE EVIDENCE AND REASONS FOR OTHER STUDIES

Population based studies provide the best method of assessing the epidemiology of STIs that are not generally confined to core groups, but such studies are rare. In the United Kingdom, the only investigation of this type was the second National Survey of Sexual Attitudes and Lifestyles (NATSAL 2000), which explored the reported population experience of STI infection, and the prevalence of C. trachomatis. This showed that 69% of women diagnosed with C. trachomatis had attended GUM services, whereas only 30% diagnosed with PID had attended GUM services. This emphasises the role of services other than GUM in the management of STIs, and highlights the need to widen the scope of STI surveillance. However, the complex, expensive probability sampling technique used in NATSAL is not feasible for routine data collection. While not as accurate as population studies, primary care surveillance could provide estimates of the burden of morbidity within a group that closely corresponds to the general population. Almost 80% of the UK population consult a general practitioner at least once a year, and other primary care settings, such as family planning clinics are regularly attended by young people. A number of studies have provided information on the burden of STIs in primary care. One recent study, the Chlamydia Screening Studies (ClaSS) project, explored C. trachomatis prevalence in a general practice registered population aged 16–39 between 2001 and 2002, and included the collection of a limited range of variables for each patient. However, since these studies are unique they cannot be used for surveillance.

Infrequent panel surveys are a source of surveillance data. The Morbidity Statistics from General Practice (MSGP) was undertaken every 10 years and the last study, MSGP4, was undertaken in 1992. The dataset was derived from attendances over a 1 year period at 60 general practices in England and Wales, and represented a 1% population sample. Although not a random sample, the dataset is broadly representative of the general population in terms of age, sex, marital status, socioeconomic status, smoking behaviour, and burden of disease. However, although this is a potentially good source of data, it only gives an insight into the prevalence and determinants of incidence within the population at the time of the study. Nationally representative, prospective data are required to produce the timely insights into STI epidemiology that are needed to guide health policy.

Large prospective primary care surveillance datasets have become available over the past decade. The General Practice Research Database (GPRD) and MediPlus UK Primary Care Database are based on general practice attendances. The GPRD covers 6.4% of the UK population, is broadly similar to the Office of National Statistics (ONS) census in terms of age and sex, and includes data on diagnosis and treatment. MediPlus contains clinical and prescribing data from approximately 1.7 million patients who have attended 140 UK general practices since 1991 and is representative of the general population in terms of age, sex, and regional distribution. In addition, the Royal College of General Practitioners’ General Practice Research Unit undertakes continuous sentinel surveillance in 72 practices covering 600 000 people in England and Wales and collects demographic and diagnostic data. However, these datasets cannot be easily adapted to the specific requirements of STI surveillance because they do not capture data on reproductive history, contraceptive history, or sexual behaviour. Clinical samples are not taken, and the methodologies cannot be modified. In addition, the cost of using these datasets can be high. Information from family planning clinics is only consistently
can be placed within the context of the incidence (box 2), so that the diagnoses are compiled concomitantly with the demographic, and behavioural factors that influence STI surveillance. Information on factors that influence STI occurrence, and acceptability of diagnosis is likely to be limited because many are either unassessed, or collected once every 10 years; prospective studies are designed for general disease surveillance; little or no behavioural, demographic, and reproductive health data are collected; and many studies do not use standard diagnostic criteria. A new primary care STI surveillance system would help resolve these problems and create a resource to inform sexual health planning. Here we explore the attributes of such a system.

REPEATED PANEL SURVEYS OF PRIMARY CARE ATTENDERS: A WAY FORWARD?

The aims of the survey would be to estimate prevalence, and change in prevalence over time. The need for the timely collection of detailed data, together with a clinical sample suggests that a methodology based on a substantial population sample is inappropriate. A point prevalence sampling technique would increase efficiency and would be surprisingly small: a random sample of about 4000 would give a sufficiently small: a random sample of about 4000 would give a representative sample of the population. A point prevalence sampling technique would increase efficiency and would be surprisingly small: a random sample of about 4000 would give a representative sample of the population.

Table 1: Number of people required to detect differences in prevalence*

<table>
<thead>
<tr>
<th>Difference between populations (%)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td>−3</td>
<td>−653</td>
</tr>
<tr>
<td>−2</td>
<td>482</td>
</tr>
<tr>
<td>−1</td>
<td>2314</td>
</tr>
<tr>
<td>+1</td>
<td>4023</td>
</tr>
<tr>
<td>+2</td>
<td>1239</td>
</tr>
<tr>
<td>+3</td>
<td>653</td>
</tr>
</tbody>
</table>

*Calculations assumed a random sample, 5% two sided significance level.

Potential problems associated with a panel survey, the main concern being the comparability between the two general practice age/sex register and the general population. Young men are less likely to be registered with a general practitioner than young women. For patients between the ages of 15 and 44 attending general practice the median contact days remain relatively constant over time at 6.4 per 100 people per week and 9.8/100 people per week, for males and females respectively.17 This panel survey technique is an idealised model and would have to be adapted to specific situations as it may not be feasible or appropriate to collect detailed data in some situations. In addition, the focus on general practitioners may make such a study difficult to implement at a time of demanding health care needs. The framework for such an initiative is beyond the scope of this paper, but the principles of harmonised surveillance system that would allow a rapid evaluation of STI epidemiology and sexual health within and between countries.

CONCLUSIONS

The close relation between surveillance intelligence, disease prevention, and public health policy was highlighted by the Department of Health’s “Getting ahead of the curve.” At present, STI surveillance is limited by the relative lack of information from primary care: initiatives capable of identifying and evaluating emerging health care need to be available from NHS family planning clinics and Brook Advisory Centres. The data, which are not validated and confirmed to contraceptive method, age, and sex of each patient at the first contact in the financial year, are reported to the Department of Health on the KT31 return.
developed. The method discussed here could allow an efficient assessment of STI prevalence, sexual health, and health service access behaviour. Such developments will be invaluable to future primary care STI surveillance, but no single method can effectively undertake surveillance. Other opportunities are evolving such as NHS electronic health records, a longitudinal record of patient health and health care, developments that have to be evaluated and assimilated into STI surveillance to complement existing knowledge. Creativity, innovation, and vision will be needed but it is only by doing this that we will be able to get ahead and stay ahead of the curve.

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Authors’ affiliations
I Simms, A-K Hurtig, G Hughes, K A Fenton, PHLS, Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, UK
P A Rogers, PHLS Statistics Unit

Correspondence to: Ian Simms, PHLS, Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ, UK; isimms@phls.org.uk

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HIV

New drugs for treating drug resistant HIV-1

A Isaac, D Pillay

Clinical management of virological failure remains an important and difficult issue for HIV physicians

One of the major barriers to successful treatment of HIV-1 infection is the emergence of drug resistant virus. The greatest impact of resistance is that it limits the effectiveness of subsequent antiretroviral combinations following initial drug failure. At a population level, more than 50% of patients who fail therapy do so with viruses resistant to drugs within at least one class of drug, with 15–20% with resistance to drugs within all three currently available classes (Health Protection Agency, unpublished data).

Therefore, there is an urgent requirement for new drugs with activity against such resistant species. Over the past year or so, there has been a welcome upsurge in data presented on new drugs, both within existing classes and new classes, with the promise of more effective therapies for HIV resistant viruses (see table 1).

NUCLEOSIDE/NUCLEOTIDE ANALOGUES

Nucleoside analogue drugs have been the mainstay of HIV therapy since zidovudine was first licensed in 1988, and it is not surprising that resistance to this class of drugs is most common at a population level (Health Protection Agency, unpublished data). Despite some specific signature mutations for individual nucleoside analogues, there is increasing evidence for cross resistance.

Table 1 Some new drugs recently approved and in clinical development with possible activity against resistant viruses

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Stage of development</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Approved</td>
<td>Active against TAMs</td>
</tr>
<tr>
<td>Amdoaxorv (DAPD)</td>
<td>Phase I/II</td>
<td>Active against various NRTI associated mutations, but not necessarily multidrug resistance</td>
</tr>
<tr>
<td>Alavudine</td>
<td>Phase I/II</td>
<td>Activity against TAMs and antagonism with AZT and d4T</td>
</tr>
<tr>
<td>TMC120</td>
<td>Phase I/II</td>
<td>Second generation nNRTIs active against nNRTI resistant viruses</td>
</tr>
<tr>
<td>TMC125</td>
<td>Phase I/II</td>
<td>Activity against K103N/V106/L100I mutations. Mutations at 181 codon confer high level resistance</td>
</tr>
<tr>
<td>PIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Phase III</td>
<td>Favourable resistance profile in PI naive, but unclear cross resistance pattern in PI experienced. Good side effects profiles</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Phase I/II</td>
<td>Likely to be effective in patients with experience of multiple protease inhibitors</td>
</tr>
<tr>
<td>Fusion inhibitors</td>
<td>Phase I/II</td>
<td>Active against multidrug resistant viruses</td>
</tr>
</tbody>
</table>

Mårdh P-A

Simms I

P A Rogers

NW9 5EQ, UK

PHLS, Communicable Disease Surveillance Centre,
61 Colindale Avenue, London NW9 5EQ, UK;
isimms@phls.org.uk
between certain drugs, such as ZDV and d4T, as well as the emergence of mutations conferring broad cross resistance, such as the 69 insertions, and the Q151M constellation of mutations within reverse transcriptase. Interesting data have been presented for alvulidine, a thymidine analogue previously shown to have considerable toxicity in the clinic. Now reassessed at lower doses, activity is observed in patients with ZDV/d4T resistance (up to five thymidine analogue resistance associated mutations, TAMS) although antagonism between these thymidine analogues is observed when used in combination. More data are awaited for this rejuvenated compound. Amadoxovir (DAPD) is a new nucleoside analogue prodrug whose oral administration leads to a rapid in vivo conversion to (−)-α-dioxalane guanosine (DXG). Resistance to this drug in the laboratory appears to involve the K65R and L74V mutations, similar to those observed for abacavir (although ABC failure is rarely associated with these mutations in the clinic). Phase I/II studies demonstrate a reasonable activity of this drug against nucleoside analogue resistant viruses, although more data are needed before clarifying its potential role. However, activity in vitro is compromised by the multinucleoside resistance mutation Q151M together with changes at amino acid 69 of reverse transcriptase, which may limit its role in higher nucleoside analogue experienced patients. The drug attracting most excitement at present is the recently approved nucleoside analogue tenofovir, which appears to be unencumbered by the toxicity problems of its cousin, adefovir. As for many other drugs, the HIV mutations in reverse transcriptase associated with reduced activity in the clinic are not necessarily those selected by tenofovir in the laboratory (K65R). This is because the drug has been most widely tested in drug experienced patients in whom resistant virus already exists and predictors of poor response can be identified. Thus, common nucleoside analogue resistance mutations such as M41L, L210W (possibly a key marker in this respect), and T215Y appear to reduce, although not negate, clinical efficacy; nevertheless, the widespread use of tenofovir in salvage therapy and promising first line treatment trial data suggest that it represents an important addition to our antiretroviral armoury.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

The phenomenon of extensive cross resistance between nNRTIs is one of the more widely accepted truths of HIV drug resistance. Moving to the small binding site for this group of drugs within the viral reverse transcriptase, the key mutations in this regard are K103N, T181C, and G190A/E, all of which compromise nevirapine, efavirenz, and delavirdine responses, and this cross resistance represents a major limitation of the class as a whole. However, two new compounds, TMC 125 and TMC120, appear to have activity against such resistance viruses, both in vitro and in vivo. Another compound (capravirine) demonstrated activity against a virus bearing the K103N or V106A or L100I single mutation, although high level resistance to this drug was reported in the presence of mutations at codon 180. It appears not so much that different patterns of resistance mutations are observed with these new nNRTI drugs, but rather that emergence of resistance is much slower than existing nNRTI drugs—note that single dose nevirapine in pregnancy is sufficient to select for resistant mutants—and that the well recognised nNRTI mutations have a marginal, and possibly clinically irrelevant, impact on fold susceptibility. It is argued that these properties are a function of the unique structures of these second generation nNRTIs, in the context of binding to the RT enzyme. We look forward towards more extensive clinical trial data for both these drugs.

PROTEASE INHIBITORS

Issues of resistance and cross resistance are particularly pertinent to the protease inhibitor class of drugs. Many claims have been made on the apparent uniqueness of resistance patterns for specific drugs, based on in vitro data, which do not then translate into clinical benefit for that drug in PI experienced patients. Two new PIs have now undergone initial clinical evaluation. Atazanavir (ATZ), soon to be available within an expanded access programme, demonstrated different resistance profiles when used in PI naive or PI experienced patients. In the former group, resistance emerges with the 150L and A71V mutations. This is a unique combination since amprenavir resistance mutations include a different amino acid change at position 50 (namely, 150V), although the A71V mutation is a polymorphism (not infrequently observed in the absence of PI therapy). By contrast, in PI experienced patients, some level of cross resistance between atazanavir and other PIs was apparent, and therefore the utility of this drug as a second line PI may be limited. Clinical data for this scenario are awaited at the time of writing. Clinical data have also been presented for tipranavir, which shows potency against viruses containing a large variety of PI resistant mutants in vitro. Clinical activity was indeed observed in PI experienced patients, with a suggestion that a very large number of PI resistant mutations were required to compromise activity. More work is required to further clarify such “clinical cut offs” whereby clinicians can be guided on the likely effect of this new drug in a patient with existing PI resistant virus.

FUSION INHIBITORS

Data are now emerging from the trials of T-20 (enfuvirtide), the first fusion inhibitor to enter the clinic. Since the phase III trials were undertaken in heavily pre-treated patients it is not surprising that failure rates (lack of full suppression) were relatively high overall; however, this affords the opportunity to characterise the emergence of resistance. Data from phase II studies demonstrate that the majority of such failure patients had mutations in the gp41 region targeted by the drug—namely, between amino acids 36–45, which indeed confirms that activity of the drug is mediated through the proposed mechanism. Since variation in this region is very rare in T-20 naive patients, including those infected with non-subtype B viruses, it can be assumed that previous RT inhibitor and PI therapy will not compromise T-20 activity itself. The key issue with use of T-20 in salvage therapy will therefore be the choice of other active drugs to combine with it. Of interest, the second generation fusion inhibitor T-1229 appears to be active against most T20 resistance mutants, although this is based on in vitro evidence alone.

CONCLUSION

Despite the undoubted success of antiretroviral therapy clinical management of virological failure remains an important and difficult issue for HIV physicians. Since such patients often have drug resistant virus, the choice of new combinations is often based, at least to some extent, on our knowledge of resistance characteristics of available drugs. We have summarised the data on a whole series of new drugs within existing and new classes. After some years of promising in vitro data, these drugs have demonstrated promise in clinical trials, with particular interest focused on unique resistance patterns, or the slow development of resistance. As further clinical trial data are presented for new drugs, it is important for HIV physicians to ask two specific questions. Firstly, what are the resistance patterns at baseline, which define success or failure of this new drug in antiretroviral experienced patients? and, secondly, does the resistance correlates of failure when used as a first line drug? It is answers to these questions that will contribute to identifying the optimal role of these promising new drugs in routine clinical practice.

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References
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