Until recently, few persons from countries with limited resources had access to life-preserving but expensive antiretroviral (ARV) drugs. On 1 December, WHO launched the 3 by 5 Initiative to expand treatment access programmes in resource-limited settings providing so as to provide 3 million persons with ARVs by the end of 2005.

Although it is universally recognized that HIV therapy has remarkably reduced HIV-related mortality, many critics are concerned that the widespread use of ARVs has the potential to select drug-resistant populations of HIV strains. With the WHO commitment through the 3 by 5 Initiative, to increase access to ARVs in resource-limited countries, additional concerns are being raised regarding the likelihood that HIV resistance could be accelerated by ART access programmes, if ARV use is inappropriate or adherence to ARVs is poor.

When resistance emerges, an anti-HIV drug that was once effective becomes less able to fight the virus. That drug will need to be switched to a more expensive second-line alternative. The consequences of drug resistance include treatment failure, increased direct and indirect health costs, transmission of resistant strain to treatment-naive subjects and the need to develop new anti-HIV drugs. Thus, HIV resistant strains has been recognized as a serious threat to the efficacy of current and future HIV treatments.

It is not clear that resistance will emerge or spread more rapidly in countries with limited resources. However, there are clear concerns that resistance could become a major public health problem. It is problematic to quantify this threat because, until now, it has been extremely difficult to collect reliable, standardized and comparable global data on the level of HIV drug resistance and its transmission.

Data on the prevalence of resistance among treatment-naive subjects in countries where ARV drugs have been available for years ranged from 5% to 27%. For example, a study performed in Boston in 1999 indicates that resistance mutations were present in 18% of the treatment-naive subjects examined. Recent data from 17 European countries showed that 10% of the untreated patients carry drug resistant virus. Very little data is available from countries that will implement ART programmes in line with the 3 by 5 target.

Ethically, the threat of increased levels of resistance must not be an excuse not to deliver life-prolonging therapy to persons in need as it has not been a reason to delay universal access in developed countries. Instead, what is required is monitoring HIV drug resistance and developing approaches to reduce its emergence and spread. WHO and its partners intend to collect reliable and updated information on the prevalence of HIV resistant strains among treated and untreated subjects, as ARVs become widely available.

Four major public health questions need to be answered:

- What is the level of resistance to ARVs in circulating HIV strains?
- How is HIV drug resistance prevalence changing over time in different areas?
- Is increased treatment availability causing a rapid rise in HIV drug resistance?
- Can adherence-enhancing interventions slow the emergence of resistant HIV strains?
To address these questions, WHO and its partners established the following objectives within its 3 by 5 Strategy:

- to track HIV drug resistance prevalence among treated and untreated subjects and assess its geographical and temporal trend.
- to understand more completely determinants of resistance, especially the adherence to treatment and factors that undermine it.
- to identify ways to minimize the appearance of resistance, its evolution and spread; and
- to provide information to international and country-level policy-makers through a rapid and easily accessible dissemination system.

The 3 by 5 Initiative must seek to address all these questions. Towards that goal, and in broad terms, WHO has identified the need to strongly support a

- global surveillance of ARV resistance through:
  - development and implementation of surveillance systems at national and regional level that measures HIV drug resistance prevalence among newly diagnosed and treatment-naïve subjects. This target population is easily reachable in any epidemiological setting and can provide information on drug resistance transmission level;
  - development and implementation of a monitoring systems to measure HIV drug resistance prevalence among treated persons;
  - review of the available resistance data that have been produced globally up to now;
  - establishment and strengthening of a global network of experts and laboratories involved in HIV resistance testing and support technology transfer in limited-resources countries;

Within the WHO/UNAIDS 3 by 5 strategy, data from ARV resistance surveillance will guide patient support activities and capacity building plan (see briefs on Capacity building and Mobilizing communities).

The implementation of the WHO program needs the involvement of the global HIV/AIDS scientific and public health community. As a first step, WHO has established a coalition of 50 of the world’s experts in the public health, policy, clinical management, laboratory and science of HIV drug resistance (HIVResNet), to develop guidelines on how to conduct resistance surveillance in different setting and population groups.

On 1 December 2003, WHO Guidelines for HIV Drug Resistance Surveillance in newly diagnosed and treatment-naïve HIV subjects was on the WHO website. The Guide addresses important aspects of a good quality surveillance system like sampling, data collection, laboratory testing, data management and analysis, quality control and ethical issues. The development and implementation of the HIV-resistance surveillance system will be primarily supported in high-burden countries where ARVs, currently not widely available.

The acquisition of data on HIV drug resistance prevalence in those areas will allow a base-line picture that can be compared with data obtained over the time. By contrast, HIV drug resistance monitoring in treated subjects will be supported in those resource-limited countries access to ARVs has been established for 2-3 years.

A surveillance system that will allow monitoring of HIV drug resistance and its determinants is an essential component of the 3 by 5 Initiative. Early recognition of the appearance and spread of drug resistance, with the definition of the relevant determinants calls for rapid prevention action and support to affected patients. No effort should be spared to ensure that progress made in the access to treatment for HIV patients in both developed and resource-poor countries is not jeopardized by a massive increase of drug resistance.

**Milestones:** By 2004, WHO and its partners plan to develop and implement systems to measure HIV drug resistance in treatment-naïve persons in 20 countries and to monitor HIV drug resistance among treated persons in 5 countries. By 2005 a total of 40 and 15 countries, respectively, will have the surveillance and monitoring systems implemented.