

When the drugs don't work: HIV is growing more resistant to treatment

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When Nathan Clumeck last year examined 100 people in the Democratic Republic of the Congo who had begun HIV treatment in the previous 12 months, he was shocked by what he found. Thirty of them had virus strains that resisted the standard medicines given to new patients.

The current approach to treatment in the developing world is contributing to growing drug resistance, warns Prof Clumeck, head of infectious diseases at Belgium's St-Pierre University Hospital. "We are creating a virological time bomb."

The development is emerging at a time when sharply escalating funding from the international community is increasing treatment in poorer countries – and, paradoxically, this wave of treatment is part of the problem. Initiatives include most recently President George W. Bush's approval this week for a \$48bn (£24bn, €31bn) five-year programme of which the bulk is to be spent on combating Aids.

Drug resistance is of concern because the spiralling economic burden of HIV, the escalating costs and difficulties of using alternatives and the increasing likelihood of a resistant virus spreading across Africa and beyond come just as the research for new drugs and prevention techniques risks losing momentum. With 3m patients in low- and middle-income countries receiving antiretroviral therapy (ART) for HIV, the rising absolute numbers carrying resistant strains of the virus have important implications for governments in poor countries – as well as for richer ones that receive immigrants and sponsor treatment in their countries of origin.

The issue is triggering growing international attention. David Heymann, an assistant director-general of the World Health Organisation, told a UK House of Lords committee recently: "We have

drugs going out in massive quantities ... and there are not systems in countries that are [in place and are] monitoring resistance to these drugs.”

The question will be discussed in detail at the 17th international Aids conference that begins this weekend in Mexico City – alongside a series of recent setbacks to researchers trying to develop vaccines and microbicide gels to reduce the risk of HIV infection and new drugs to treat it. **Roche** of Switzerland last month said it was withdrawing from HIV research, while **Merck** of the US recently cancelled one such treatment project; poor results have also left it with no HIV vaccine under test.

Resistance to HIV – as with tuberculosis, malaria and multiple microbial infections – is nothing new. In the US, some studies have shown that up to a quarter of “treatment-naive” patients not yet receiving drugs carry resistant forms of the virus. Nor does it necessarily spell disaster. There are more than 25 different combinations of medicines developed over the past decade, offering doctors in the west a range of alternative “second-line” and subsequent “salvage” drug cocktails to reduce side-effects and fight HIV in spite of resistance.

But there are important differences with the new epidemic of HIV drug resistance in the developing world. In richer countries, the phenomenon has emerged over two decades, fostered by the prolonged use of a single “mono-therapy” drug when there was no alternative. In poorer countries, however, it has appeared far more rapidly.

Since Médecins Sans Frontières began offering HIV services at its South African clinic in the poor Cape Town district of Khayelitsha five years ago, for example, the international medical charity estimates that 22 per cent of its patients no longer respond to first-line antiretroviral therapy.

Patients in the developing world who in the past were left to die are now able to take advantage of more recent medical advances by receiving combinations of different drugs that are more effective and reduce this risk of resistance. But their options remain much more limited than for those living in the west. Where patients in richer countries receive treatment tailored to their needs, with detailed medical examinations and expensive testing, in poorer nations the trade-off for providing accelerated access since the start of the decade has been a “public health approach”. This involves simplified methods using a standardised and far narrower range of drugs, without the need for the costly laboratory analysis and intensive medical scrutiny associated with individually tailored care.

The result is that most newly diagnosed HIV patients in poorer countries receive types of first-line therapy that are not now prescribed in the west, including efavirenz and nevirapine. These are from a class of drugs called non-nucleoside reverse transcriptase inhibitors (NNTRIs) which, while allowing cheap and effective treatment for many patients in the short term, may also trigger greater long-term resistance.

Not everyone sees resistance as a problem. A recent series of studies produced under the auspices of the World Health Organisation concluded that fewer than 5 per cent of patients in Asia, Latin America and Africa carried virus resistant to these medicines, justifying their continued use as first-line therapy. But Prof Clumeck is sceptical. “It’s a very useful discourse to show that donors are not wasting their money,” he says. The studies may be unrepresentative, he adds – and resistance typically takes several years to develop whereas, in most countries examined, treatment began only in the last two to three years.

The snag is that so little data on resistance currently exist for first-line therapies, let alone for alternative fallback treatments. Large donors including the United Nations-backed Global Fund to Fight Aids, TB and Malaria have accelerated treatment but not imposed accompanying monitoring. “I think this is likely to be the single most important problem in the field,” says Kevin Frost, chief executive of the Foundation for Aids Research, which has received funding from the Dutch government to establish networks to monitor HIV resistance in Asia. “It’s far more complicated and slow to develop surveillance infrastructure for monitoring resistance than for treatment.”

Selina Lo, medical co-ordinator in Geneva for MSF, which has been in the forefront of HIV treatment in developing countries, says: “We don’t really have the capacity to do resistance studies. Monitoring capacity is really poor. It requires so much investment.”

In the absence of more reliable data, one proxy indicator of resistance is poor “adherence” – the

extent to which patients take their medicine consistently and at the recommended doses. Some studies have suggested that poorer countries have been able to achieve rates of above 90 per cent, similar or even above those in the west. But a systematic review published last year in *PLoS Medicine*, an academic journal, suggested that across 70,000 patients in 13 sub-Saharan African countries treated during 2000-07, on average only just over 60 per cent were still taking medicine two years after they were first enrolled in a clinic.

Treatment rates...

% with advanced HIV receiving antiretroviral therapy* (2007)

Namibia	88
Botswana	79
Rwanda	71
Zambia	46
Swaziland	42
Malawi	35
Uganda	33
Ethiopia	29
Ivory Coast	28
South Africa	28
Nigeria	26
Cameroon	25
Mozambique	24
Dem. Rep. Congo	24
Zimbabwe	18

... and retention

% with HIV still on treatment 12 months after start of antiretroviral therapy* (2007)

Mozambique	97
Cameroon	96
Nigeria	95
Zimbabwe	93
Rwanda	91
Ivory Coast	89
Zambia	88
Uganda	97
Botswana	87
Namibia	71
Ethiopia	70
Dem. Rep. Congo	70
Malawi	69
Swaziland	64
South Africa	53

Source: UNAIDS
* selected sub-Saharan countries

"A worrying number of patients in sub-Saharan Africa who need ART are lost from treatment programmes," concluded the researchers from Boston and Johannesburg, who argued that true retention rates might be lower still because clinicians with more disappointing results are less likely to publish them.

Of the 40 per cent who stopped seeking treatment, some did so because they were diagnosed too late and died. But many others were "lost to follow-up", a catch-all term that includes many patients who are still alive and – having started and then stopped taking medicines – allowing the virus to survive in more resistant form. The first-line therapies used as standard in developing countries have unpleasant side-effects that increase the likelihood patients will stop taking them regularly. HIV develops resistance to the NNRTIs more easily than to more recently launched classes of drug – and resistance is to the entire class of NNRTIs, closing off alternative treatment options.

More generally, much HIV treatment to date in poor countries – including sub-Saharan Africa, which has two-thirds of the world's cases – has been "gold-plated": it is provided by organisations such as MSF with expatriate doctors, funding and support far beyond the quality available in most government clinics. The more that antiretroviral therapy programmes are extended in remote rural areas for the estimated two-thirds of HIV-infected people who require treatment but are not receiving it, the greater the risks become of poor adherence. Supplies of drugs may be irregular and patients who eke out an existence on the land may struggle to keep appointments with healthcare workers, while a lack of adequate food or social support can discourage them from taking their medicines as prescribed.

Other factors are also contributing to greater drug resistance in developing countries than traditionally seen in the west. Weak public health systems mean patients have sought private medical advice, and sometimes taken medicines that are not recommended, or have been unable to pay for and take the prescribed drugs consistently.

Another great short-term success in Africa in recent years also brings long-term risks: a preventative dose of nevirapine to expectant mothers with HIV and their newborns sharply reduces the risk that the child contracts the virus from an infected mother. But it also triggers resistance, preventing the drug's future use to treat them. Equally, the lack of HIV drugs tested for use in children – a problem that scarcely exists in the west but that affects 2m children, largely in Africa – means pills designed for adults are crudely cut or split, in a way that may not provide the appropriate dosage.

Also in danger of stimulating drug resistance in developing countries are poor-quality therapies. The US Department of Justice recently claimed in court filings – vigorously rejected by the company – that **Ranbaxy** of India, a large exporter of generic HIV medicines, had "adulterated" drugs sold via the US into the developing world.

A study this spring by **Abbott Laboratories** of the US suggested that Indian generic companies'

copies of Kaletra, Abbott's antiretroviral drug, were not absorbed in the same way in the body, raising questions about how effective they would prove.

Elsewhere, unpublished data in Thailand point to significant levels of resistance in patients using NNRTIs produced by the state pharmaceutical company, which has failed to pass quality control tests from any external regulatory agency. The resistance may in part be because Thailand has been treating more patients for longer. But it also points to one necessary policy response to fight resistance: tougher international scrutiny of plants that produce HIV medicines and an assurance for countries buying them that quality is consistent.

A second need is for innovative medical programmes to boost drug adherence in poor countries. A third possible approach is a shift in the treatments used. Prof Clumeck calls for a switch directly to make current second-line therapies into the first-line option. But with many of these drugs still on patent, that implies substantial extra costs unless developers slash prices.

In any case, a final immediate issue is a need for greater efforts to strengthen the monitoring of resistance – something called for in the UK's House of Lords report late last month.

One message unites the prophets of rising drug resistance: they all argue that the trend should not justify slowing down the current expansion of HIV treatment to the developing world. As Kevin de Cock, director of the HIV department of the World Health Organisation, says: "If the message is not already on a bumper sticker, it ought to be: 'It's better to be alive with drug-resistant virus than dead with drug-sensitive virus'."

Still, as Mr Frost argues: "Resistance is an entirely predictable end-point. If it starts to spin out of control, it's going to be difficult to get a handle on."

A PORT SEEKS A PLACE FOR FRANK TALK

Veracruz, a steamy port on the southern Gulf of Mexico that is the largest city in the Mexican state of the same name, bears the official designation "Heroic" for its long history of resistance to invaders. These days it is on the front line of a different battle: the country's fight against HIV/Aids, **writes Ronald Buchanan.**

"We have the highest mortality rate from Aids of any state in the country," says Aurora Díaz, head of Coversida, a citizens' group that promotes education on the issue. From her office in the Veracruz university medical faculty where she co-ordinates research, Dr Díaz recalls the despair, bordering on panic, she and her public hospital colleagues felt when the first cases of Aids were identified in Veracruz just over 20 years ago.

In the pre-internet age and with the media kept on a tight rein by the one-party system that then ruled Mexico, "we didn't know where to look for information, much less know how to provide any for the population at large", Dr Díaz says. "Of the first five patients that were diagnosed, four were at an advanced stage and died within a year. There was no medicine, precious little information – but I realised that something had to be done."

That "something" was to found Coversida. Since then, knowledge has spread, but so too has Aids. Veracruz, the nation's leading port, has doubled in size since Mexico's economy opened to the world. Migrants from all over the country and beyond flocked in – as did the sex industry. Free trade and paid-for sex have proved a potent cocktail.

Coversida is one of several similar groups that sprang up at the same time across the country. Like the citizens' groups that emerged from the devastating 1985 Mexico City earthquake, they opened the first chinks in the armour of one-party rule. While the government sat on its hands, ordinary people for the first time tackled big social issues by themselves.

The government has since taken action of its own. Antiretroviral drugs are available free to those without medical insurance and are administered at a growing number of state clinics – one of them just a block away from Dr Díaz's office. But the citizens' groups still have a big role to play, says José Luis López of the San José de Guadalupe Foundation in Nezahualcoyotl, a working-class suburb of Mexico City. So does David Alberto Murillo, president of the Mexico City-based Amigos contra el Sida ("Friends against Aids").

While noting that the health ministry's budget for the fight against Aids rose by almost 40 per cent this year to \$150m (£76m, €96m), Mr Murillo says nothing is being done to help patients who suffer severe side-effects from antiretroviral medication. Nor are efforts being made to adopt new alternatives. "But the biggest gap is in education," he adds.

For years Mexico was like Victorian Britain, with a priggish veneer on an underworld bacchanal. Homophobia remains rife and the sexual abuse of children is often covered up. "When you can't talk frankly about routine sexual matters, it's difficult to get the message about Aids across to people," says Mr Murillo. "Sex education in schools is severely restricted by teachers' reticence."

Mr Murillo favours sex education in primary schools. "About 50 per cent of the children in primaries abandon the school system after that," he says. "Once that happens, they're effectively abandoned."

In Nezahualcoyotl, Dr López adds: "People have got to learn to speak frankly about sex and shake off their prejudices."

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