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**MAT**

Medication-assisted therapy. Treatment approach that uses opioid substitution therapy (OST) with methadone, buprenorphine, or other agonists or antagonists to support antiretroviral therapy for opioid-dependent patients with HIV infection.

**Methadone**

Opioid agonist in liquid form which has long been used for OST. Methadone-maintenance therapy (MMT) is a widely used approach to treat heroin and other opioid dependency.

**NSP**

Needle and syringe programmes. A core component of harm reduction. NSPs provide sterile injection equipment, and get used equipment out of use and safely disposed. An entry point into treatment and care for many heavy users.

**Opioids**

Large class of agents, licit and illicit, derived from active compounds of the opium poppy, *Papaver somniferum*. Opium paste or base is the raw plant extract, generally smoked. Morphine is major active component. The diacetylated form of morphine is heroin. Opioids in common medical use include morphine, codeine, demerol, dilaudid, and oxycontin. Potent analgesics that mimic agonists (endorphins) at endogenous receptors in mammalian brain, they all have capacity to induce dependence.

**Risk environment**

The structural, social, political, and environmental contexts and influences that can drive or reduce risk practices and vulnerabilities.

We want this Series to be an inflexion point in the history of injecting drug use and HIV infection. We want to see the latest scientific evidence trigger a more humane response to this, one of the most preventable sources of HIV disease. And we want to see inappropriately aggressive, state-sponsored hostility to drug users replaced by enlightened, scientifically driven attitudes and more equitable societal responses. We recognise that the barriers to these hopes are many and

deeply rooted across continents and cultures. But we also know that science can catalyse unprecedented social change, and unprecedented social change is what is needed for the millions of marginalised people infected with HIV who use drugs.

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## 12 myths about HIV/AIDS and people who use drugs

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People who use drugs too often face stigma, discrimination, and mistreatment in HIV prevention, treatment, and care. Some societies consider such users less deserving of compassion than others with HIV who are not drug users, because users' health problems are self-inflicted or their substance use is judged as a moral or personal failing. Even among health-care providers, many preconceptions prevail about people who use drugs and are infected with HIV. What are these myths (panel)?

*Drug users are non-compliant*—In a meta-analysis of adherence to antiretroviral therapy from 38 studies

and nearly 15 000 patients, of whom 76% were drug users, overall adherence was similar to that reported for other populations with sexual exposure histories that were taking antiretrovirals.<sup>1</sup> Better outcomes with antiretrovirals were associated with being on opioid-substitution therapy, receiving psychosocial support, or both. The meta-analysis concluded that HIV-positive drug users tended to be inappropriately assumed to be less compliant and unlikely to achieve desirable treatment outcomes than non-drug-using cohorts.

*Drug users do not respond as well to antiretrovirals as do non-drug-using patients*—A comparison of survival rates in 3116 antiretroviral-naive patients started on antiretrovirals (in Vancouver, Canada), of whom 915 were injecting drug users, showed similar all-cause mortality by 84 months after starting antiretrovirals.<sup>2</sup> In a multivariate time-updated Cox's regression, the hazard ratio of mortality did not significantly differ between injecting drug users and those who did not inject drugs (1.09, 95% CI 0.92–1.29). Injection drug use was not associated with decreased survival in patients who had started on antiretrovirals.

*Drug users are difficult to study and have poor retention rates in cohorts, making prospective research studies with drug users difficult or impossible*—The first phase 3 HIV-vaccine efficacy trial in a developing country was the AIDS-VAX B/E (VaxGen) trial in 2546 injecting drug users in Bangkok, Thailand.<sup>3</sup> Although the vaccine failed to elicit protection, the trial was successfully conducted with 2295 (90.1%) of participants retained at 36 months and an overall HIV incidence of 3.4 per 100 person-years. Such excellent retention shows the willingness of people who use drugs to enrol and stay in prospective studies.

*Drug users are more concerned about getting high than using injecting equipment safely*—In a study of 760 participants who used a supervised injecting facility in Vancouver, Canada, more consistent use of the facility was associated with safer injecting behaviours than was less consistent use, including less syringe re-use (odds ratio [OR] 2.16, 95% CI 1.48–3.16), use of clean water for injecting (3.15, 2.26–4.39), safer disposal of syringes (2.22, 1.54–3.20), and less injecting outdoors (2.99, 2.13–4.21).<sup>4</sup> Given the choice, people who use drugs preferred safe and clean equipment.

*Drug users don't have much sex; their HIV risks are largely or entirely from needle sharing*—One of us (SAS) with others<sup>5</sup> explored sex differences in HIV seroconversion in 1447 male and 427 female injecting drug users in Baltimore, MD, USA, over 10 years. Incident HIV infection in men was associated with young age, recent needle sharing with multiple partners, and daily use; but the incidence of HIV infection was double in men engaging in recent sex with other men compared with men who did not engage in this behaviour. For women who injected drugs, risks related to heterosexual sex were more closely associated with HIV infection than were drug-related risks.

#### Panel: 12 myths about HIV/AIDS and people who use drugs

- 1 Drug users are non-compliant
- 2 Drug users do not respond as well to antiretrovirals as do non-drug-using patients
- 3 Drug users are difficult to study and have poor retention rates in cohorts, making prospective research studies with drug users difficult or impossible
- 4 Drug users are more concerned about getting high than using injecting equipment safely
- 5 Drug users don't have much sex; their HIV risks are largely or entirely from needle sharing
- 6 If drug users keep using, it is almost inevitable that they will acquire HIV infection
- 7 Unlike gay men or sex workers, drug users don't have strong communities, so community interventions are unlikely to work
- 8 Rates of drug use are higher among minorities in the USA and other industrialised countries
- 9 Needle exchanges encourage drug use
- 10 Methadone (or buprenorphine) treatment just exchanges one drug for another
- 11 People who use stimulants are all heavy, out-of-control users who won't change their risky behaviours
- 12 Fear is an effective deterrent for drug use

*If drug users keep using, it is almost inevitable that they will acquire HIV infection*—The most recent data from the US Centers for Disease Control and Prevention (CDC) on new HIV infections in the USA among men and women who inject drugs show there has been a decline in the number of new cases in injecting drug users of both sexes from 1998 to 2007,<sup>6</sup> although the prevalence of injecting drug use has been stable or modestly increasing across the USA since 2000.<sup>7</sup>

*Unlike gay men or sex workers, drug users don't have strong communities, so community interventions are unlikely to work*—The Thai Drug Users Network organised hundreds of drug users across Thailand to protest human rights violations against people who use drugs during the 2003–04 crack-down which led to thousands of drug users being executed.<sup>8</sup> The Network engaged in local and regional advocacy, and successfully obtained a Global Fund grant.

*Rates of drug use are higher among minorities in the USA and other industrialised countries*—According to the 2006 National Survey on Drug Use and Health,<sup>9</sup> African-Americans and whites have similar patterns of illicit drug use. According to the 2006 findings from the Monitoring the Future study, African-American students in the 8th, 10th, and 12th grades have substantially lower rates of use



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for most illicit drugs than do white students.<sup>9</sup> A 2009 CDC report found that white injecting drug users had higher rates of needle-sharing than did minority-group users.<sup>10</sup> Incarceration rates for offences related to substance use, however, do differ by race; with the highest rates of incarceration being among African-Americans.<sup>11</sup>

*Needle exchanges encourage drug use*—There is no evidence to suggest that, after the introduction of a needle-exchange programme, rates of drug use or starting to inject increase.<sup>12</sup> A study of 600 injecting drug users in Alaska, USA, randomised users to receive access to needle exchange compared with training on buying needles and syringes from pharmacies, to test whether access to needle exchange increased the frequency of injection.<sup>13</sup> There was no difference in the amount of injecting drug use between these two groups at 6 or 12 months ( $p=0.0001$ ).

*Methadone (or buprenorphine) treatment just exchanges one drug for another*—A Cochrane review that included 1969 participants in six randomised trials showed that methadone was superior to non-pharmacological approaches in retaining patients in treatment, and in reducing heroin use, measured by self-report and urine or hair analysis (relative risk 0.6, 95% CI 0.56–0.78).<sup>14</sup> Another Cochrane review showed that medium and high doses of buprenorphine were more successful than placebo alone at decreasing heroin use.<sup>15</sup>

*People who use stimulants are all heavy, out-of-control users who won't change their risky behaviours*—Mausbach and colleagues,<sup>16,17</sup> showed reductions in sexual-risk

behaviour by HIV-negative heterosexuals and by HIV-positive men who have sex with men, despite ongoing use of methamphetamine. These behavioural interventions show that users of stimulants can reduce their risks for sexual acquisition of HIV infection, even if their drug use continues.

*Fear is an effective deterrent for drug use*—The US Institute of Medicine report reviewed the evidence for fear-based campaigns as deterrents for substance use and found they had no effectiveness.<sup>18</sup>

Biases and stigma against those who use drugs, are drug-dependent, or have a history of injecting are common. Such biases have no place in the practice of medicine or in the allocation of public health resources. The myths about HIV acquisition and people who use drugs are straightforwardly countered by scientific evidence, but like so many forms of prejudice, they persist despite the evidence. It is past time for these prejudices to change. Providers, decision makers, and all engaged in the global fight against HIV infection have an obligation to examine biases against people who use drugs, learn the facts beyond the myths, and let evidence drive responses.

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## PARP inhibition in BRCA-mutated breast and ovarian cancers

More than 1 million women globally are diagnosed with breast or ovarian cancer every year, and 5–10% of them carry a germline mutation in *BRCA1* or *BRCA2*.<sup>1–3</sup> Inside the complex of DNA repair machinery, the *BRCA* proteins play a crucial role via homologous recombination, while poly(ADP)-ribose polymerase (PARP) is the key component in base-excision repair of DNA. Preclinical studies showed that inhibition of PARP would lead to selective and significant killing of *BRCA*-mutated cancer cells, a phenomenon described as synthetic lethality that is not observed in cells with intact *BRCA* function.<sup>4,5</sup>

In *The Lancet* today are two phase 2 studies of olaparib, an oral PARP inhibitor, for patients with advanced breast cancer or recurrent ovarian cancer who harbour *BRCA1* or *BRCA2* mutations. Both studies are well conducted in multiple high-quality centres around the world. The accrual rate of about 0.5 patients screened per centre per month for these relatively uncommon study populations is impressive. Using olaparib 400 mg twice daily, Andrew Tutt and colleagues<sup>6</sup> reported a tumour response rate of 41% for patients with breast cancer, while William Audeh and co-workers<sup>7</sup> reported a tumour response rate of 33% for patients with ovarian cancer. Additionally, both studies reported similar clinical benefit rates of 52% and median progression-free survival of about 6 months. Severe toxicities were rare in both studies, with only one treatment discontinuation due to treatment-related adverse events in each trial.

These remarkable tumour response rates have undoubtedly proven the concept that a PARP inhibitor

can suppress tumour growth in patients with *BRCA*-mutated cancers. All enrolled patients were heavily pretreated and had poor prognoses. The response rates were significantly better than the expected rate of 20% or less with cytotoxic chemotherapy.<sup>8,9</sup> It seems that PARP is the right target, and olaparib has successfully hit the target in both cancers. These two studies are the first to show successful PARP inhibition in two different cancers with identical pathogenic genetic defects. The findings contribute to the evolving concept of genetic classification of cancer. Traditionally, we rely on histology and site of origin to classify and treat cancers. With emerging targeted agents aimed at specific molecular defects (eg, rituximab for CD20-positive lymphoma, trastuzumab for HER2-overexpressed breast cancer, or gefitinib for non-small-cell lung cancer with *EGFR* mutation), molecular classification of cancer will invariably become more informative than conventional classification for the guidance of targeted therapy, and *BRCA* mutation might be integrated into the classification of breast and ovarian cancer.

However, today's results might not reflect the complete picture. Successful targeted therapy relies on specific inhibition of a driving molecule or pathway and, upon inhibition, the typical tumour response rate is in the range of 50–70% and the disease control rate is more than 80% (table). If the synthetic lethality generated by the inhibition of PARP in *BRCA*-mutated cancer suppresses tumour growth as proposed by preclinical models, a similar magnitude of response should have

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