Implications for a policy of initiating antiretroviral therapy in people diagnosed with human immunodeficiency virus: the CAPRA research programme

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Scientific summary

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Scientific summary

Background

The human immunodeficiency virus (HIV) is endemic in men who have sex with men (MSM) in many settings, including the UK (Beyrer C, Baral SD, van Griensven F, Goodreau SM, Chariyalertsak S, Wirtz AL, Brookmeyer R. Global epidemiology of HIV infection in men who have sex with men. *Lancet* 2012;**380**:367–77). Antiretroviral therapy (ART) is now highly successful in reversing the effects of HIV and has reduced death rates in successfully treated people to levels that are not much higher than those in the general population. Given that there are reductions in infectivity of people on ART, there is widespread interest in the potential effect of ART in controlling the HIV epidemic. However, there are a number of areas, including the UK, where ART use is high among MSM and yet incidence has not declined; therefore, its potential impact on epidemics in MSM has been questioned. In this programme of research we set out to address what would be the population-level clinical effectiveness, and cost-effectiveness, of the introduction of a policy of initiating ART in all people diagnosed with a HIV infection. We performed a series of studies and calibrated a model of HIV transmission, progression and the effect of ART in MSM in order to inform this question. As there is strongest evidence for substantial ongoing transmission for MSM, we concentrated on this group in modelling but our studies also involved heterosexual populations, particularly black Africans, for whom HIV prevalence is high.

Programme of work and findings

Programme component: ASTRA study

The Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study is a cross-sectional study of > 3000 people diagnosed with a HIV infection. The primary aims were to assess the association of ART use and self-reported viral load (VL) status with condomless sex (CLS), and to assess attitudes to the early use of ART among people not yet on treatment. The study found no evidence that being on ART was associated with increased levels of CLS, or CLS with partners of serodifferent (unknown or negative) HIV status. There was evidence that, among MSM on ART, those with self-reported suppressed VL were more likely than those without to have CLS, and CLS with serodifferent partners, but levels of CLS among MSM with self-reported suppressed VL did not exceed those among MSM not on ART. ART/self-reported VL was not significantly associated with CLS among heterosexual individuals. In addition, there was a high accuracy of a self-report of undetectable VL, when compared with the latest clinic-recorded value.

We also assessed in 281 ART-naive people, with a high cluster of differentiation 4 (CD4) count, their attitude towards ART initiation and the motivations. The percentage of participants agreeing with statement 1, that they would want to start ART now to slightly reduce risk of serious illness, was 50%, and the proportion agreeing with statement 2, that they would want to start now to reduce infectiousness even if there was no health benefit, was 45%. Overall, 32% of participants agreed with both statements 1 and 2, 31% agreed with one of the two statements, 13% disagreed with both statements and 25% were uncertain.

The study has also provided information on quality of life in people infected with HIV compared with the general population. This analysis suggests that quality of life is moderately, but significantly, reduced among people infected with HIV, mostly related to increased levels of depression and anxiety, although the extent to which being infected with HIV is a cause of such symptoms is uncertain. The study is proving to be a rich source of information in a variety of areas, including sexual behaviour, recreational drug use, status disclosure, age and health, and factors associated with ART adherence and virological success. On recreational drug use, the study found that half of the 2248 HIV-diagnosed MSM surveyed had used

recreational drugs in the past 3 months and that about one-quarter had used at least three types of drugs during that time period. Drug use and polydrug use were very strongly associated with higher numbers of sexual partners and with all measures of CLS. In terms of ageing-related issues, the study found that the prevalence of physical functional problems among people infected with HIV increased with age, but the prevalence of symptom distress did not, and the prevalence of depression and anxiety decreased with age. In contrast to this, a longer time with diagnosed HIV was strongly related to higher prevalence of all adverse health and symptom measures, independently of age. The ASTRA questionnaire data were also being linked to routine clinic data to enable the assessment of the association between factors assessed in the questionnaire and virological outcomes. Socioeconomic disadvantage and depression were factors found to be strongly related to non-adherence to ART, and to poorer VL outcomes among people on ART.

Programme component: AURAH study

The Attitudes to, and Understanding of, Risk of Acquisition of HIV (AURAH) study is a cross-sectional study assessing sexual risk behaviour among people undiagnosed with a HIV infection (overwhelmingly HIV negative) from groups with high HIV prevalence (black Africans and MSM) seen at sexual health clinics. The study will help us understand the context in which sexual HIV transmission risk is occurring. In total, the 2630 participants included 1484 MSM and 548 black African men and women. Among all MSM, the prevalence of any recreational drug use in the past 3 months was 55%, the prevalence of CLS with multiple partners (two or more) in the past 3 months was 29% and the prevalence of CLS with an unknown or HIV-positive partner in the past 3 months was 33%. Recreational drug use and markers of low socioeconomic status were found to be independently associated with CLS measures [including sexually transmitted infection (STI) diagnosis in the past year] and high partner numbers (reporting five or more new sexual partners in the past year and group sex in the past 3 months). Furthermore, among MSM who reported sex in the past 3 months ($n = 1340$), the prevalence of depressive symptoms (Patient Health Questionnaire-9 score of ≥ 10) was 12%. Depressive symptoms were found to be independently associated with CLS measures (including STI diagnosis).

Programme component: CIPHER study

The Cognitive Impairment in People with HIV in the European Region (CIPHER) study involved assessment of neurocognitive impairment (NCI) in people infected or not infected with HIV. It indicated that levels of NCI in HIV-positive MSM in the UK could be overestimated on the basis of previous research, and suggested that diagnosed deficits may not be related to HIV alone. These results suggest that a re-evaluation of current diagnostic criteria for NCI in HIV, including an increase in the level of deficit required to meet the criteria, may be necessary.

Programme component: START transmission risk behaviour substudy

The US National Institutes of Health and other funders funded the main Strategic Timing of Antiretroviral Therapy (START) clinical trial (of immediate vs. deferred ART); however, the enhancement of the START risk behaviour data collection and the analysis and writing up of those findings falls under the Comprehensive Assessment of the Prevention Role of Antiretroviral therapy (CAPRA) funding programme described here in this report. In this substudy, transmission risk behaviour was assessed in a group of > 4000 ART-naive people at baseline in the START trial. The proportion reporting CLS with a partner of unknown or serodifferent status was higher in MSM, at 20%, than in either heterosexual men (10%) or women (14%). We also found that MSM reporting CLS with a partner of unknown or serodifferent status were more likely to report a greater number of partners. For example, 6% of MSM reporting CLS with a partner of unknown or serodifferent status had more than five partners in the previous 2 months. In MSM, factors associated with having CLS with a partner of unknown or serodifferent status in our study included younger age, more recent HIV diagnosis, recreational drug use, region of recruitment and being of Hispanic, black or another ethnicity rather being white or Asian. The main START trial will allow the study of the effect of ART initiation on sexual behaviour in the context of a randomised comparison (this work is not discussed here, given that its scope is outside the CAPRA programme).

Programme component: PARTNER study

The Partners of People on ART: a new Evaluation of the Risks (PARTNER) study is studying the risk of sexual transmission of HIV between serodifferent partners having CLS when the positive person is on ART with VL suppression.

Programme component: modelling and cost-effectiveness analysis

Modelling of the clinical effectiveness and cost-effectiveness of increased HIV testing and immediate ART at diagnosis in MSM in the UK was carried out using an individual-based model calibrated to multiple data sources. In the first phase of our modelling we assessed the HIV epidemic in MSM in the UK to the present, in particular the role of ART in limiting transmission. Our study throws light on the apparently paradoxical increase in HIV infection incidence among MSM epidemics over a period when ART coverage and viral suppression has been increasing. Our analysis suggests that it is the counter-effect of concomitant increases in CLS among MSM as a whole that has resulted in a net increase in incidence, despite a positive influence of ART in reducing incidence. The work highlighted the enormous limiting effect that condom use is having on the epidemic in MSM. In the second phase of modelling, the predicted effects of increases in HIV testing and initiation of ART at diagnosis were evaluated and, in particular, we addressed what is needed for the incidence of HIV in MSM to be reduced to < 1 per 1000 person-years from the current level of six times that. We find that for increased testing and earlier ART use to lead to a HIV infection incidence of < 1 per 1000 person-years, the overall proportion of MSM living with HIV who are virally suppressed on ART needs to increase from the current level of < 60% to 90%, without increases in CLS. The incremental cost-effectiveness ratio associated with the fourfold increase in levels of HIV testing and ART at diagnosis required to provide this increase from < 60% to 90% is £20,000 if we assume that current ART prices are maintained. However, this value falls to £3500 if we assume that the price of ART will fall to 20% of its current level as a result of the introduction of generic drugs.

Conclusions and outstanding issues

Our cost-effectiveness analysis suggests that ART initiation at diagnosis is likely to be cost-effective in MSM. The fact that the main START trial has now demonstrated that ART initiation is beneficial, even in people with CD4 cell counts of > 500/μl, supports ART initiation in all people diagnosed with a HIV infection. The key outstanding issues for prevention of new infections that emerge from our modelling work are (1) that HIV testing rates in those people having CLS should be increased and (2) that continued efforts to minimise risky CLS are needed [by 'risky' we mean that it is a possibility that the two partners are serodifferent for HIV and neither partner is taking antiretroviral drugs either as treatment for a HIV infection or as pre-exposure prophylaxis (PrEP) to prevent a HIV infection]. In addition to these two issues, a third is that of the cost-effectiveness of PrEP, which was evaluated in UK settings in light of the recent positive findings from the Pre-exposure Option for reducing HIV in the UK (PROUD) and Intervention Preventive de l'Exposition aux Risques avec et pour les Gays (IPERGAY) studies, using the model calibrated as part of this programme. These three areas (testing, CLS and PrEP) are intertwined and the future research agenda for 2016 onwards is clear – we need to find the means of providing an optimal HIV prevention environment with as efficient use of resources as possible, but bearing in mind that resources spent now could avert much greater costs in future years.

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