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Abstract

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

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Background: More than 100,000 people in the UK are living with a human immunodeficiency virus (HIV) infection. There are currently estimated to be around 4000 people newly infected in the UK per year, mostly men who have sex with men (MSM). It has become increasingly clear that antiretroviral therapy (ART) used to treat people infected with HIV also has a profound effect on infectivity. At the initiation of the programme, it was the policy in the UK to initiate ART in people when their cluster of differentiation 4 (CD4) count was approaching 350/μl.

Objectives: To assess what would be the effectiveness and cost-effectiveness of a policy of immediate initiation of ART at diagnosis among MSM, taking into account the potential reductions in new infections.

Design: We calibrated an individual-based model of HIV transmission, progression and the effect of ART in MSM, informed by a series of studies on sexual behaviour in relation to ART use and the transmission risk in people with viral suppression on ART, and by surveillance data collected by Public Health England.

Setting, participants and interventions: The series of studies used to inform the model included (1) the Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study, a cross-sectional self-administered questionnaire study of people diagnosed with HIV attending eight HIV outpatient clinics in the UK (2011–12); (2) the Cognitive Impairment in People with HIV in the European Region (CIPHER) study, a study of levels of neurocognitive impairment in HIV-positive ASTRA participants and people from HIV clinics in Rome, Copenhagen and Minsk; (3) the Attitudes to, and Understanding of, Risk of Acquisition of HIV (AURAH) study, a cross-sectional self-administered questionnaire study of individuals who have not been diagnosed as HIV-positive attending 20 genitourinary medicine clinics across the UK (2013–14); (4) a substudy of sexual behaviour among individuals enrolled in an open-label multicentre international randomised trial (from 2013) of immediate versus deferred ART (to CD4 cell counts of 350/μl) in people with CD4 cell counts of > 500/μl [the Strategic Timing of Antiretroviral Therapy (START) trial]; and (5) Partners of People on ART: a new Evaluation of the Risks (PARTNER), an observational multicentre longitudinal study of HIV serodifferent heterosexual and MSM couples, in which the HIV-positive partner is on ART (2010–14).

Main outcome measures: The main outcome measures were the clinical effectiveness and cost-effectiveness of a policy of immediate initiation of ART at diagnosis.

Results: Based on data from studies (i)–(v), we estimated from our modelling work that increases in condomless sex (CLS) among MSM as a whole may explain the increase in HIV infection incidence in MSM epidemics over a time when ART coverage and viral suppression increased, demonstrating the limiting effects of non-condom use on the HIV epidemic among MSM. Accordingly, an increase in the overall

proportion of MSM living with HIV who are virally suppressed on ART from the current level of < 60% to 90% without increases in CLS was required to achieve a reduction in the incidence of HIV among MSM to < 1 per 1000 person-years. 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% was £20,000 if we assumed continuation of current ART prices. However, this value falls to £3500 if we assume that ART prices will fall to 20% of their current cost as a result of the introduction of generic drugs. Therefore, our evaluation suggests that ART initiation at diagnosis is likely to be highly cost-effective in MSM at a population level, particularly accounting for future lower ART costs as generic drugs are used. The impact will be much greater if levels of HIV testing can be enhanced.

Limitations: It was necessary to make some assumptions beyond the available data in order to extrapolate cost-effectiveness through modelling.

Conclusions: Our findings suggest that ART initiation at diagnosis is likely to be cost-effective in MSM. Of note, after this programme of work was completed, results from the main START trial demonstrated benefit in ART initiation even in people with CD4 cell counts of > 500/μl, supporting ART initiation in people diagnosed with a HIV infection.

Future work: There is a need for future research into the means of increasing the frequency with which MSM test for HIV.

Funding: The National Institute for Health Research Programme Grants for Applied Research programme.

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Glossary

Condomless sex Sex without a condom.

Couple-years of follow-up Length of time over which couples are followed up.

Polydrug use Use of more than one drug at the same time/within the same time period.

Seroconcordant couple A couple in which both partners are of the same human immunodeficiency virus status.

Serodifferent/serodiscordant couples A couple in which one partner is human immunodeficiency virus positive and the other is human immunodeficiency virus negative.

Seropositioning/strategic positioning Assignment of the receptive/insertive role during sex according to human immunodeficiency virus status to reduce transmission risk.

Serosorting Sex with only partners of the same human immunodeficiency virus status.

List of abbreviations

AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ASTRA	Antiretrovirals, Sexual Transmission Risk and Attitudes
AURAH	Attitudes to, and Understanding of, Risk of Acquisition of HIV
CAPRA	Comprehensive Assessment of the Prevention Role of Antiretroviral therapy
CD4	cluster of differentiation 4
CIPHER	Cognitive Impairment in People with HIV in the European Region
CLS	condomless sex
CLS-D	condomless sex with one or more serodifferent partners
CYFU	couple-years of follow-up
GUM	genitourinary medicine
HIV	human immunodeficiency virus
HPTN	HIV Prevention Treatment Network
IQR	interquartile range
MSM	men who have sex with men
NCI	neurocognitive impairment
NIHR	National Institute for Health Research
PARTNER	Partners of People on ART: a new Evaluation of the Risks
PHQ-9	Patient Health Questionnaire-9
PrEP	pre-exposure prophylaxis
RNA	ribonucleic acid
START	Strategic Timing of Antiretroviral Therapy
STI	sexually transmitted infection
VL	viral load

Plain English summary

In the UK, the human immunodeficiency virus (HIV) is mainly transmitted by sex without a condom. Without antiretroviral therapy (ART), HIV wipes out key immune cells called cluster of differentiation 4 (CD4) cells. In the past, the CD4 cell count was allowed to drop to a certain, still-safe, level before starting ART, in order to balance the risk of side effects. Recent studies have shown that ART also dramatically reduces the risk of HIV transmission to a sexual partner, and an alternative policy of treating everyone with HIV from the time of their diagnosis has been considered. In this programme of work we focused on men who have sex with men (MSM), and investigated if a change in treatment policy – to treat all MSM infected with HIV from the time of diagnosis – would be an efficient use of NHS resources given the increased use of drugs. From our findings, we estimated that the benefits (i.e. preventing future HIV transmission) are likely to be greater than the cost of increased drug use and, therefore, that a change in treatment policy is likely to be cost-effective among MSM. Following the completion of our programme of work, a large clinical trial investigating whether or not treating people with a higher CD4 cell counts versus treating people with lower but still safe CD4 cell counts [the Strategic Timing of Antiretroviral Therapy (START) trial] has more health benefits, found that individuals infected with HIV have health benefits from starting earlier ART. These findings support our conclusion that ART initiation in MSM diagnosed with HIV is likely to be cost-effective. The results from the START trial are not presented in this report in any detail because only a substudy of sexual behaviour among START participants was investigated as part of the Comprehensive Assessment of the Prevention Role of Antiretroviral therapy (CAPRA) grant. This report presents the results from our cost-effectiveness analysis and the studies used to inform this analysis.

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.

Funding

Funding for this study was provided by the Programme Grants for Applied Research programme of the National Institute for Health Research.

SYNOPSIS

Of note, this work is a summary of, and does not include verbatim duplication of, the original article: Phillips AN, Cambiano V, Miners A, Lampe F, Rodger A, Nakagawa F, *et al.* Potential impact on HIV incidence of higher HIV testing rates and earlier antiretroviral therapy initiation in MSM. *AIDS* 2015;**29**:1855–62.[1]

The human immunodeficiency virus (HIV) is endemic in men who have sex with men (MSM) in many settings, including the UK.[2] Antiretroviral therapy (ART) is now highly successful in reversing the effects of HIV and has led to death rates in successfully treated people that are not much greater than those of the general population.[3,4] Given that there are reductions in infectivity of people on ART,[5] there is widespread interest in the potential effect of ART in controlling the HIV epidemic,[6] but there are a number of areas, including the UK, in which ART use is high among MSM, and yet incidence has not declined[7–10] and its potential impact in epidemics in MSM has been questioned.[9,11] In the Comprehensive Assessment of the Prevention Role of Antiretroviral therapy (CAPRA) programme of research that started in 2010 we set out to address what would be the population-level clinical effectiveness, and cost-effectiveness, of introduction of a policy of initiating ART in all people with a diagnosed HIV infection. 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.

There are several factors in considering a change in policy and its potential clinical effectiveness and cost-effectiveness. First, it is important to understand how low the transmission rate is from a person on ART with a suppressed plasma viral load (VL) to a HIV-negative partner. Second, it is important to consider overall trends in condomless sex (CLS) and, in particular, whether or not therapeutic success of ART will lead to further increases in CLS as fear of having HIV is diminished. A third consideration is that a high proportion of new infections come from men who are not yet diagnosed, and in many cases men who have only just been infected.[12–14] This might seem to limit the influence that ART can have in reducing new HIV infections in MSM. We should also consider how high the rate of HIV testing is, and how rapidly those who are infected become diagnosed and linked to care. Then there is the threshold for initiation of ART; this has to take into account the evidence for clinical benefit of starting ART even in people with very high cluster of differentiation 4 (CD4) cell counts and a low HIV VL, and here there is no consensus on interpretation of current evidence.[15–17]

At the start of the programme this was an area of ongoing research with two trials – the Strategic Timing of ART (START)[18] and Benefits and Risks of Early Antiretroviral Therapy in HIV-infected Adults in Abidjar, Côte d' Ivoire: Randomized Controlled Trial (ANRS 12136 TEMPRANO)[19] – having randomised ART-naive people with a high CD4 cell count to initiate or defer ART. At the start of the programme, in the UK the absolute threshold for ART initiation was a CD4 cell count of 350/μl[17] although the threshold is higher in other guidelines.[15] In addition, it was important to consider offer and uptake of 'treatment as prevention', defined in a community statement as when a person is offered to start taking ART – at a time when it is not unequivocally thought to be needed for the person's health – in order to reduce the risk that they can transmit HIV.[20] Furthermore, we had to consider not just if people initiate and remain on ART, but their levels of adherence and viral suppression.[21] The development of drug resistance and onward transmission of resistance, and its potential to undermine benefits of ART, should also be taken into account.

Considering cost-effectiveness, costs of HIV care have been mainly driven by costs of ART drugs and it is important to consider potential future changes in costs of ART as branded drugs go off patent and much cheaper generic drugs are introduced. Accordingly, a cost-effectiveness analysis based around a model calibrated to multiple data sources that takes all these factors into account was investigated. In this programme of research we performed five separate empirical studies (*Figure 1*). These studies addressed (1) attitudes towards immediate ART initiation, associations of sexual behaviour with ART use and self-reported VL status, and assessment of sociodemographic circumstances and lifestyle factors, mental and physical health and well-being among people living with a HIV infection [Antiretrovirals, Sexual

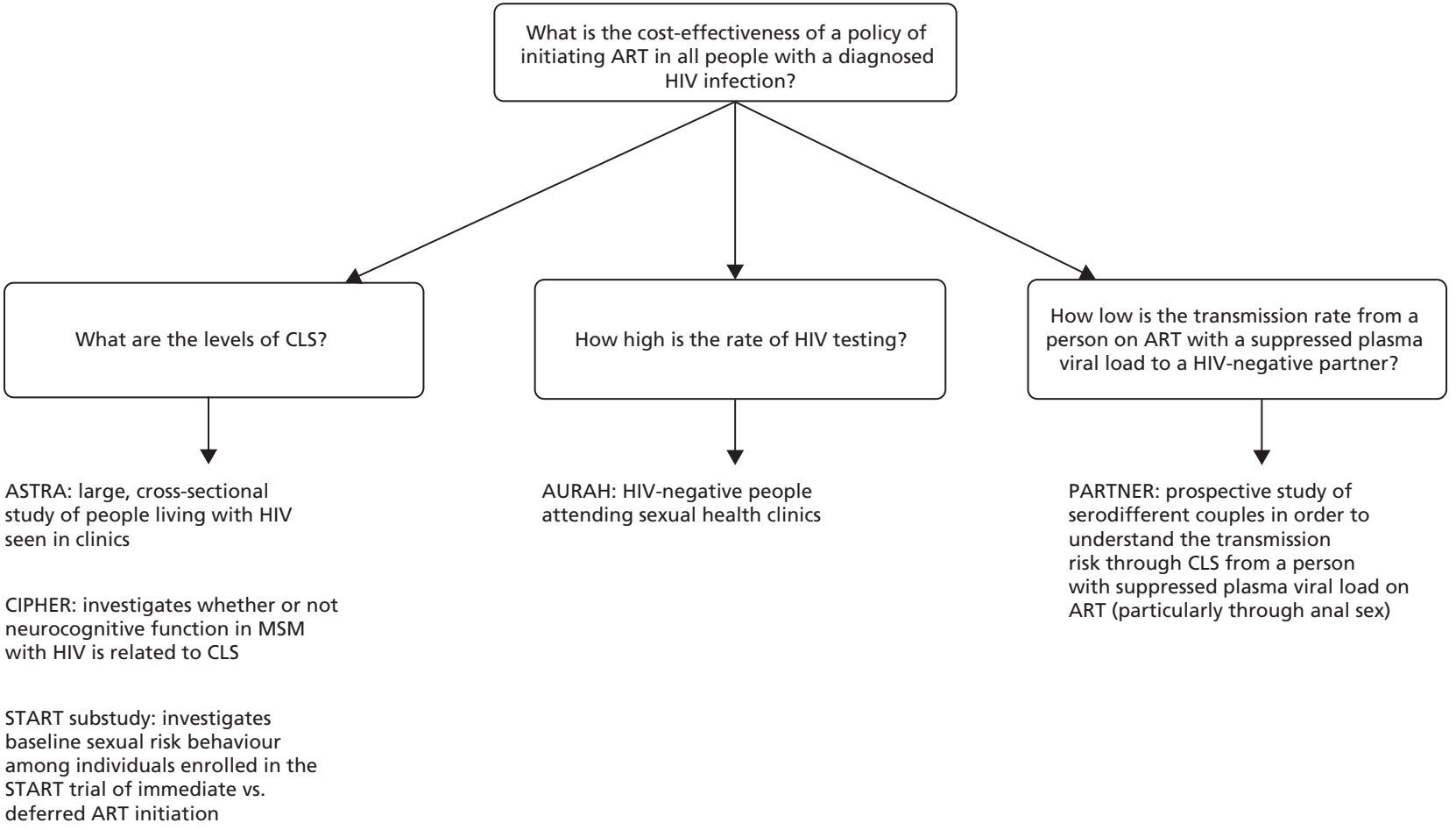

FIGURE 1 Diagram to show how individual study components relate to the overall modelling aim of the programme.

Transmission Risk and Attitudes (ASTRA)]; (2) the relationship between HIV and neurological conditions [Cognitive Impairment in People with HIV in the European Region (CIPHER)]; (3) the prevalence of CLS and HIV testing among people at risk of HIV acquisition, and associated factors, including attitudes towards HIV infection transmission risk in the context of ART [Attitudes to, and Understanding of, Risk of Acquisition of HIV (AURAH)]; (4) prevalence of sexual risk behaviour and associated factors among people enrolled in a large randomised trial (START transmission risk behaviour substudy); and (5) the risk of HIV transmission through CLS from a person with supressed plasma VL on ART, in a prospective study of serodifferent couples [Partners of People on ART: a new Evaluation of the Risks (PARTNER)].

The cost-effectiveness was estimated using an individual-based simulation model calibrated to data from studies 1–5. Our cost-effectiveness modelling consisted of two phases. The first phase was done to understand the influences on the epidemic up to the present time and, in particular, to quantify the impact that ART had already made in reducing new infections. Findings from this modelling phase indicated that increases in CLS among MSM as a whole explains the increase in HIV infection incidence in MSM epidemics over a time period in which ART coverage and viral suppression increased, demonstrating the limiting effects of non-condom use on the HIV epidemic among MSM. The second phase was carried out to make predictions of the future numbers of infections and quality-adjusted life-years to be lived in MSM, according to various potential changes in ART policy, and to assess the cost-effectiveness of such policies; in particular, we predicted the impact of increased HIV testing and immediate ART use in order to inform what levels of testing and early treatment would be needed to reduce the incidence of HIV infection among MSM to < 1 per 1000 person-years. Findings from this modelling phase indicated that an increase in the overall proportion of MSM living with HIV who are virally suppressed on ART from the current level of < 60% to 90% is needed, without increases in CLS, to achieve such a reduction in HIV infection incidence. 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%, was £20,000 if we assume continuation of current ART prices. This value falls to £3500 if we assume that the ART prices will fall to 20% of their current cost, as a result of the introduction of generic drugs.

Although the CAPRA programme was planned to strengthen and inform the public health approach to understanding, and later reducing, ongoing high rates of sexual HIV transmission in the UK, and the management of treatment for HIV-positive people, the research studies all overlapped with some of the most important community concerns that directly affect the health and well-being of people living with a HIV infection.

We review our current findings from each component study and discuss the strengths, weaknesses and overall implications of this programme.

The Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study

This section describes the ASTRA study, a cross-sectional questionnaire study of 3258 people with a diagnosed HIV infection, recruited from eight HIV outpatient clinics in the UK from February 2011 to December 2012, with a response rate of 64% (see Speakman *et al.*[22]). The questionnaire was self-completed and confidential, and included sections on demographic factors, socioeconomic circumstances, HIV-related factors (including self-reported VL status), lifestyle factors, health and symptoms, and a detailed section on recent sexual behaviour. In addition, the latest clinic-documented VL and CD4 cell count results that had been communicated to each participant were recorded. The study also had a longitudinal component, in which questionnaire responses were linked (via a pseudonymised study number) to routine clinic data in six of the eight clinics, for participants who consented to this linkage.

The primary aim of the ASTRA study was to provide information on levels of CLS among people with a diagnosed HIV infection, and to address the hypothesis that ART use and perceived undetectable VL may be linked to CLS. At the time of planning the study, most previous studies addressing this question had found similar, or even somewhat lower, levels of CLS among people on ART compared with those not on ART.[23] However, there were few studies conducted after 2008, and none in the UK. This was important because advice for HIV-positive people about safe sex and the need for condom use was changed fundamentally with the 'Swiss Statement' in 2008,[24] which received great publicity but was hugely controversial at the time. The Swiss Statement asserted, with caveats, that a HIV-positive person on ART with viral suppression is not infectious to sexual partners. Therefore, at the time of planning the ASTRA study, it was hypothesised that patterns of CLS on ART may be changing and that this may have implications for HIV transmission in the UK.

Understanding patterns of CLS among people infected with HIV, and the relationship with ART use, was an important issue in the grant programme when considering the implications of a policy of early ART use in the UK. If perceived undetectable VL was associated with substantially increased levels of CLS, this could compromise the full impact of a policy of early ART on HIV transmission. This could occur if effective ART was associated with a reduction in HIV transmission risk rather than elimination of risk (although there was increasing reassurance on this point as the grant progressed, particularly with results from the PARTNER study). It could also occur if people on ART were not accurately assessing their VL status and modifying sexual behaviour accordingly, or if adherence to ART was lower among people who started treatment at earlier stages. Furthermore, any changes in patterns of CLS with ART use would have implications for the transmission of other sexually transmitted infections (STIs) as well as for HIV.

Therefore, the ASTRA study assessed the association of self-reported ART/VL status (whether or not on ART and, if so, whether or not the participant reported their latest VL was undetectable) with CLS, and CLS with a HIV serodifferent (negative or unknown) status partner(s). In addition, as information on the protective effect of suppressed VL on HIV infectiousness became established during the CAPRA programme of work, we were also able to describe likely levels of HIV transmission-risk sex – CLS carrying an appreciable risk of HIV transmission – that accounted for ART use and clinic-documented VL level as well as serodifferent partner status according to self-reported ART/VL status. The preliminary findings were presented at the HIV Drug Therapy Conference in Glasgow in 2012 and final results were published in *AIDS* (see Lampe *et al.*[25]). Among 3178 participants (the subgroup who had been diagnosed with a HIV infection for at least 3 months), use of ART was not associated with increased prevalence of CLS, or CLS with serodifferent partners, among MSM or heterosexual individuals, and ART use was associated with a

greatly reduced prevalence of higher HIV transmission-risk sex. There was some evidence that perceived undetectable VL may influence condom use among MSM: among MSM on ART, the prevalence of CLS with serodifferent partners was higher among those with a self-reported undetectable VL (15.2%) than among those without a self-reported undetectable VL (9.8%). However, for both of these 'on ART' groups, prevalence of CLS with serodifferent partners was lower than the corresponding prevalence for MSM not on ART (18.8%), suggesting that any effect of perceived undetectable VL on reducing levels of condom use among HIV-diagnosed MSM was modest at the time of the study and would not undermine the effect of early ART on HIV or STI transmission. The prevalence of HIV transmission-risk sex (serodifferent CLS, together with either 'not on ART' or a clinic-recorded VL of > 50 copies/ml) among all 3178 participants (MSM and heterosexuals) was 3.2% overall: 16.1% for people not on ART, 0.6% for those on ART with self-reported undetectable VL and 4.2% for those on ART without self-reported undetectable VL. Therefore, the results supported the prevention role of ART offered to all people infected with HIV, and emphasised the need to focus on HIV infection/STI prevention among those not on ART.

The study also demonstrated a high level of accuracy of self-report of undetectable VL status among people infected with HIV in the UK. Considering all 2678 ASTRA study participants on ART, of those 2137 who self-reported undetectable VL, clinic-recorded VL was ≤ 50 copies/ml for 96.4% of participants and < 1000 copies/ml for 99.3% (see Sewell *et al.*[26]). These findings are encouraging with regard to the implications for decisions about sexual behaviour and condom use that are based on perceived undetectable VL, as HIV transmission is extremely unlikely when the VL is < 1000 copies/ml. Overall, accuracy of knowledge of the latest VL level (whether or not the self-reported result agreed with the latest value from the clinic record) varied according to demographic, socioeconomic, and HIV- and health-related factors. In particular, accuracy was considerably lower among those with socioeconomic disadvantage, those who were not fluent in English, those who reported non-adherence to ART and those with psychological symptoms. This suggests that there may be specific groups who may benefit from increased levels of support concerning knowledge and experience of treatment and care.

The second primary aim of the ASTRA study in relation to the grant programme was to assess attitudes to starting ART, among people who were not yet on treatment, in order to provide insight into the acceptability of starting treatment at a high CD4 cell count. The ASTRA study participants were asked, in the questionnaire, the extent to which they agreed with two statements: that they would want to start ART now to (1) slightly reduce their risk of serious illness and (2) reduce infectiousness to a sexual partner, even if there was no benefit to their own health. Overall, of the 281 participants with a CD4 cell count of ≥ 350/μl who had not started ART, 50% agreed with (1), 45% agreed with (2), 63% agreed with either (1) or (2), 13% agreed with neither statement and 25% were uncertain. People with a more recent HIV infection diagnosis were more likely to want to start for either reason. This was the first study to assess, in a general clinic setting, acceptability of ART at high CD4 cell counts to reduce transmission risk. These results suggested that, even in the scenario of the START trial finding only a modest clinical benefit of a strategy of starting ART at high CD4 cell counts, such a strategy was likely to be acceptable to the majority of people infected with HIV, although there would likely be a minority of participants not wanting to start ART. Results were presented at the Conference of Retroviruses and Opportunistic Infections in 2013 and published in *PLOS ONE* in 2014 (see Rodger *et al.*[27]). The ASTRA study also provided important additional information relating to sexual behaviour, health and well-being among people infected with HIV, and enabled a number of other research questions to be addressed. A programme of work on sexual behaviour among HIV-diagnosed MSM provided insight into the levels of different types of CLS and use of recreational drugs in relation to sexual behaviour, an issue that has been increasingly highlighted as a current concern.[28,29] The ASTRA study questionnaire included an inquiry on recent drug use, asking about a comprehensive list of 19 drugs, including those commonly used in party/club and 'chemsex' contexts. Of all 2189 MSM in the ASTRA study diagnosed with a HIV infection for at least 3 months, 38.3% had CLS, 16.3% had CLS with a serodifferent partner and 21.9% had CLS with only HIV-positive partners, 25.4% reported condom-protected sex only, and 36.4% reported no anal or vaginal sex in the past 3 months. Overall, 4.2% had HIV transmission-risk sex in the past 3 months.[30] This demonstrates that, although prevalence of CLS is relatively high overall among HIV-diagnosed MSM, there is a much lower

prevalence of sex with an appreciable risk of HIV transmission, indicating different implications regarding transmission of HIV compared with other STIs.

Overall, 51% of MSM had used recreational drugs in the past 3 months. Among those who used drugs, 47% had used at least three types of drugs during that time period. There were exceptionally strong associations of number of drugs used with CLS, including CLS with HIV-serodifferent and -seroconcordant status partners, with higher HIV transmission-risk CLS, and with higher partner numbers, group sex and STIs (see Daskalopoulou *et al.*[31]). These results demonstrated the high prevalence of polydrug use among MSM with HIV and emphasised the need for specialist support services in this context, and the importance of addressing drug use in HIV and STI prevention strategies. Given the high prevalence of recreational drug use among people infected with HIV, it is important for clinical care to consider the potential interactions between recreational drugs and ART drugs. Using the available linked clinic data, we showed that among MSM taking ART at the time of the ASTRA study, patterns of drug use were similar irrespective of whether or not the ART regimen used was one with a higher or lower potential for interaction with recreational drugs. This suggests that consideration of potential ART–recreational drug interactions may not currently be a priority for clinicians when deciding on an ART regimen.

Additional work on sexual behaviour among MSM in the ASTRA study investigated the association of self-reported symptoms with sexual behaviour. In comparison to MSM who reported condom-protected sex or CLS only with HIV-positive partners, levels of depression and anxiety symptoms were higher among MSM who reported CLS with serodifferent partners, and also among those who reported no sex in the past 3 months.[32] Among MSM who had sex in the past 3 months, the prevalence of CLS with serodifferent partners increased as level of symptoms increased. These results suggested that management of mental health might also play a role in HIV infection or STI prevention.

In addition to addressing questions related to HIV transmission and prevention, the ASTRA study has provided important insights into health-related issues among people living with a HIV infection. A comparison of health-related quality of life between the ASTRA study sample and a large national general population study undertaken at a similar time – the Health Survey for England[33] – found a significantly lower quality of life among people infected with HIV compared with the general population, despite most individuals in the ASTRA study being immunologically and virologically stable (see Miners *et al.*[34]). This overall difference was because of differences across all quality-of-life domains, but mostly as a result of differences in the mental health domain, with substantially higher levels of anxiety and depression apparent among people infected with HIV compared with the general population, emphasising the importance of management of mental health in this population. Estimates of reduction in quality-of-life utility score associated with having a HIV infection that were generated from this work have also fed into the modelling component of the grant, although the extent to which a HIV infection is a causal factor for quality-of-life differences cannot be proven from these analyses.

In a further ASTRA project, we assessed the association of age with health and well-being among people infected with HIV. There was a relatively high level of self-reported physical and psychological symptoms among the ASTRA study participants, assessed according to standardised symptom-based inventories. Overall, 27% of participants had depressive symptoms [assessed using the Patient Health Questionnaire-9 (PHQ-9)], 22% had anxiety symptoms [assessed using the Generalised Anxiety Disorder-7 (GAD-7) questionnaire], 56% had at least one 'physical' symptom that was causing distress [assessed using a modified Memorial Symptom Assessment Scale-Short Form (MSAS-SF) questionnaire] and 38% had a health-related functional problem [assessed using a subset of the EuroQol-5 Dimensions, 3-level (EuroQol-5D-3L) version questions]. The prevalence of physical functional problems among people infected with HIV increased with older age, but the prevalence of symptom distress did not, and the prevalence of depression and anxiety decreased with older age. In contrast to this, the length of time diagnosed with a HIV infection was strongly and positively correlated with the prevalence of all adverse health and symptom measures, and this was independent of age (see McGowan *et al.*[35]). This marked association of the longer time since HIV diagnosis with poor self-rated health is likely, in part, to be related to an earlier calendar year of diagnosis, representing an effect of diagnosis in the pre-ART and early-ART eras, but may also be as a result, specifically, of the longer time diagnosed with a HIV infection and, as such, may represent an important effect related to ageing with a HIV infection.

Using the information on the latest clinic-recorded VL for all participants, plus the additional serial VL measurements available through clinical linkage (for those participants who consented to linkage), it was possible to assess the effect of various factors on the virological success of ART. A programme of work assessed the association of socioeconomic factors on the virological outcome of ART. Among participants on ART, socioeconomic disadvantage, as assessed by a number of factors (financial hardship, rented or unstable housing, non-employment and non-university education), was strongly associated with ART non-adherence, VL non-suppression at the time of the study and subsequent VL rebound among those with initial VL suppression (see Burch *et al.*[36]). These results suggested that socioeconomic hardship is an important determinant of ART outcomes, even in the UK setting, with free universal health care, and that this effect is largely mediated through difficulties maintaining ART adherence. Among people living with HIV, the poorer socioeconomic circumstances of women and heterosexual men, compared with MSM, may explain the higher level of virological success of ART generally apparent among MSM. This hypothesis was investigated using the ASTRA study data. Socioeconomic factors appeared to explain much of the difference in VL outcomes between women and MSM, and a part of the difference between heterosexual men and MSM.[37] This work indicated the potential importance of socioeconomic factors in explaining gender disparities in ART outcomes. In addition to socioeconomic factors, the presence of depressive symptoms (assessed by the PHQ-9) was found to have a very strong association with ART non-adherence and VL non-suppression,[38] again emphasising the importance of recognition and treatment of depression in the HIV clinical setting.

The ASTRA study questionnaire also enquired about disclosure of HIV status. Overall, the prevalence of non-disclosure of HIV status (to anyone outside the health-care profession) was much lower among MSM (5.0%) than among heterosexual men (16.6%) and women (15.7%). MSM were more likely to disclose to friends than to family, whereas the opposite was true for heterosexual men and women. However, non-disclosure was not found to be associated with depression or anxiety symptoms, ART non-adherence or VL non-suppression among those on ART, suggesting that non-disclosure is not necessarily associated with adverse health outcomes (see Daskalopoulou *et al.*[39]). The ASTRA study is the largest questionnaire study of of sexual behaviour among people living with a HIV infection so far carried out in the UK. There was a reasonably high response rate (64%), although it should be appreciated that patterns of sexual behaviour and health and lifestyle issues may differ between responders and non-responders to the study. Although the study attempted to assure participants of the confidentiality of questionnaire responses and data security issues, it is worth noting that self-reported sexual behaviour may be subject to errors and biases; in particular, CLS may be underestimated as a result of factors such as social desirability bias. However, it is encouraging that we found that the prevalence of CLS with HIV-serodifferent partners among MSM in the ASTRA study was very similar to that found among MSM in the European sample of the START trial at baseline, during a similar time period; results for heterosexual participants were also similar. This gives some assurance with regard to validity of measurement. This prevalence of CLS with HIV-serodifferent partners was also similar to that found in two previous UK clinic-based studies carried out in 2004–5,[40,41] suggesting little change over calendar time. Although attitudes and behaviour in relation to condom use may have changed since the ASTRA study was conducted in 2011–12, and may be continuing to change as knowledge about transmission risk on ART is disseminated and develops, the ASTRA study results will be important in establishing a baseline against which findings of future studies of HIV-positive people can be evaluated.

Furthermore, the ASTRA study has proved to be a rich source of data on health-related issues among people infected with HIV, providing unique information on factors, such as physical and psychological symptoms and quality of life, that have implications for clinical care. To date, 10 ASTRA study papers and correspondence have been published or are in press, and there have been 14 conference presentations and four invited talks based on findings from the study.

The ASTRA study research protocol and all versions of the study documents (information sheet, consent form and questionnaire) were approved by the North West London REC 2 Research Ethics Committee (reference number 10/H0720/70). Instruments/protocols/tools/consent information for the ASTRA study are available for download from the study website (www.astra-study.org).

The Cognitive Impairment in People with HIV in the European Region (CIPHER) study

This section describes the CIPHER study, which was co-funded with the European AIDS Treatment Network. It was not part of the original CAPRA programme of work but the opportunity arose to conduct the work as an adjunct to the ASTRA study. The study involved an assessment of the levels of neurocognitive impairment (NCI) in people infected and not infected with HIV in order to provide data to evaluate an important hypothesis, namely that impaired cognitive function, which has previously been associated with HIV, could cause a loss of executive function leading to higher levels of CLS among people with the disease.

There has been controversy around this issue because there is variability in the diagnostic criteria for defining NCI and, hence, uncertainty about the true extent of the problem. A number of other factors associated with living with a HIV infection (such as depression or the ageing process) might be more fundamental causes of any cognitive problems that have been found.

The specific aim of the CIPHER study was to assess the levels of NCI and associated factors in the ASTRA study participants and to combine this with a similar assessment in three European HIV clinics in order to give a more authoritative perspective of NCI across a wider region. The study used a computerised battery of neuropsychological tests that can have a number of benefits including ease of administration, reduced duration and improved user acceptability.

In total, 448 patients living with a HIV infection were recruited for this study in two of the ASTRA study clinics and separately in other HIV clinics in Rome, Copenhagen and Minsk. The ASTRA study questionnaire (translated into the local language where necessary) was completed by all of the participants along with the Cogstate (Cogstate Ltd, New Haven, CT, USA) computerised neuropsychological assessment using a customised range of tests designed to find deficits expected in people infected with HIV, with a particular focus on executive function, attention and speed of responding. An additional self-report questionnaire was also administered to measure any impairments in day-to-day living functions.

The levels of cognitive deficit were assessed using three different standardised scoring criteria taken from previous literature. The data from the ASTRA study questionnaire allowed assessment of a number of covariates including demographic (age, education and ethnicity), behavioural (smoking, alcohol and drug use), psychological (depression and anxiety symptoms) and disease-related factors (VL, CD4 cell counts, time since HIV diagnosis, ART status, time on ART and hepatitis C virus co-infection). Score results from HIV-positive patients were compared with standardised normative general population data provided by Cogstate. In the UK, scores were also compared directly with the same tests of cognitive function that were undertaken using a group of HIV-negative MSM.

The first published results from this study were based on 248 MSM recruited at the two UK clinics involved (see McDonnell *et al.*[42]). The results indicated that the prevalence of NCI in HIV-positive MSM in the UK was 21%, 31% or 40% depending on the standardised scoring criteria used. All these levels are much lower than those reported by previous studies,[43–45] and there was no difference between the deficit scores in the HIV-positive group and comparable control data from the general population or HIV-negative MSM. In addition, it was noted that large numbers of the general population would be classified as having some form of NCI based on the standard scoring criteria. It was concluded that true UK levels of impaired cognition resulting from HIV might be overestimated on the basis of previous studies. The HIV-negative control group was quite small ($n = 45$), but the lack of difference with the HIV-positive group also suggested that any previously reported deficits might not be related to HIV alone.

Further assessment of the wider group of 468 CIPHER study participants at all five European clinics has been presented in abstract form.[46] The preliminary results found that NCI was present in 35% of patients; however, it was noted that the results may be limited because of the diverse characteristics of the populations recruited at the different clinics. Nevertheless, a similar conclusion was drawn, that it may be more useful to attribute some of the cognitive and functional impairments associated with NCI classification to wider social factors and to the longer-term effects of living with HIV, such as depression.

The CIPHER study was not able to cast light on the hypothesis that possible increases in CLS might be caused by a HIV-associated neurological disorder. However, it has become clear that it may not be a fruitful question to answer, given the severe doubts about what is true HIV-related cognitive impairment. On the basis of the work undertaken here, a re-evaluation of current diagnostic criteria for NCI in people infected with HIV has been proposed, including an increase in the level of deficit required to meet the criteria. In addition, attention has been drawn to many other difficulties experienced by those living long term with HIV (as shown by the results from the ASTRA study) – including depression,[47] and misuse of drugs and alcohol[31] – that, if addressed, might improve any impairments to cognition.

Ethics approval for the CIPHER study was obtained from the National Research Ethics Service (London – Hampstead committee; reference number 11/LO/0077). Instruments, protocols, tools and consent information for the CIPHER study are available for download from the study website (www.astra-study.org).

The Attitudes to, and Understanding of, Risk of Acquisition of HIV (AURAH) study

This section describes a cross-sectional survey that collected detailed information on sociodemographic, lifestyle, health and well-being, HIV-related and sexual behaviour measures among HIV-negative (or unknown status) individuals attending 20 genitourinary medicine (GUM) clinics across the UK (see Sewell *et al.*[48]). The findings will be used to advise sexual health strategy on the acceptability of interventions, identify areas of risk behaviour that may need specific behavioural interventions and provide the best chance of successfully motivating risk reduction. In terms of this programme, the findings will be useful in helping to construct/improve further mathematical modelling to predict how different interventions would work and to provide HIV-negative counterpart data to the ASTRA study for comparative purposes.

The AURAH study was conducted to investigate the current prevalence of sexual risk behaviour, attitudes to sexual risk and HIV testing among HIV-negative adults at risk of HIV infection, and associations with sociodemographic, health and lifestyle factors.

Recruitment to the study took place between June 2013 and November 2014 at different periods in the 20 clinic sites. At the start of the study all sites were asked to identify specific clinics each week for recruitment. Clinic attendees were consecutively sampled. After 5 months, it became clear that the proportion of the populations of interest was not reaching the targets set for analytical purposes. Accordingly, clinic staff were asked to identify and recruit only MSM or individuals of black ethnicity. Once the target sample population of 1000 MSM had been achieved, the five clinic sites that had recruited the highest numbers of MSM were asked to continue sampling and to focus solely on the recruitment of MSM who were willing to participate in a follow-up longitudinal study, which commenced in November 2014 and is due to finish in March 2018.

The number of completed questionnaires finally collected was 2630 and, thus, the response rate was 60% (2630/4390) of eligible patients approached and 79% (2630/3339) of those who gave consent. Any HIV or STI tests undertaken on the day of the questionnaire, together with the result of the HIV test (negative/positive), were reported on the study log and transferred back to the study management centre on a regular basis.

Men were classified as MSM if they met at least one of the following criteria: (1) reported being gay or bisexual [including a queer, pansexual, omnisexual, fluid/open or bicurious identity (i.e. identities that are not explicitly based on attractions to one sex/gender)];[49] (2) reported having anal sex with a man in the past 3 months; or (3) reported having identified to their family, friends or workmates as being gay, bisexual and/or attracted to men. Black African men and women included participants who reported a black African ethnicity ($n = 517$) or a white and black African ethnicity ($n = 31$). In total, the 2630 participants included 1484 MSM and 548 black Africans.

The median age was 32 years for MSM and 31 years for black African men and women. The majority of MSM were born in the UK, and the majority of black African men and women were born in Africa. The majority of MSM were of white ethnicity. The level of education was very high across the demographic groups. The majority of MSM and just over half of black African men and women were employed full or part time. The majority of MSM reported always having enough money to cover their basic needs, but just under half of black African men and women reported this. Just under half of MSM reported being in an ongoing relationship, whereas most black African men and women reported an ongoing partner. Across the groups, the majority of participants were recruited for study participation in a clinic in London.

Among all MSM, the prevalence of any recreational drug use in the past 3 months was 55% and the prevalence of clinically significant depressive symptoms (PHQ-9 score of ≥ 10) was 12%.[50] The prevalence of CLS with two or more partners and CLS with an unknown and/or HIV-positive status partner (men who reported no CLS partners of unknown HIV status and only one HIV positive CLS partner who was a

long-term partner and with whom they 'thought the risks were low because their partner was taking ART', were not counted as positive for this measure) in the past 3 months was 29% and 32%, respectively. The association of sociodemographic, health and lifestyle factors with sexual behaviour measures was assessed.

Among all MSM, younger age, markers of lower socioeconomic status (non-university degree education and financial insecurity), not being in an ongoing relationship, attending a study clinic in London, higher-risk drinking and report of depressive symptoms were found to be associated with polydrug use (use of three or more recreational drugs in the past 3 months). Furthermore, polydrug use was strongly associated with all measures of CLS in the past 3 months and bacterial STI diagnosis in the past year; these associations were only slightly attenuated when adjusted for sociodemographic factors (age, ethnicity, education, sexual identity, relationship status, study region), and most remained after additional adjustment for alcohol use and symptoms of depression.

Among MSM who reported recent sex ($n = 1340$), and after adjusting for sociodemographic factors, depressive symptoms were independently associated with all measures of CLS in the past 3 months and bacterial STI diagnosis in the past year, but were not associated with having a high number of partners. After adjusting additionally for lifestyle factors (smoking, drinking and recreational drug use), most associations were attenuated but there remained significant independent associations of depressive symptoms with CLS measures and bacterial STI diagnosis. Half of all those with evidence of current depression reported receiving medical treatment or therapy for depression.[51]

Overall, 2019 participants had a HIV test on the day of the questionnaire (MSM: $n = 1227$, 82.7%; black African men: $n = 175$, 77.8%; black African women: $n = 211$, 65.3%). Overall, nine participants tested HIV positive (MSM: $n = 4$, 0.3%; black African men: $n = 3$, 1.7%; and no black African women). This included four men who indicated being MSM and three men who indicated being of black African ethnicity.

The AURAH study is the largest study of HIV-negative risk groups attending GUM clinics in the UK to date. There are, however, some important limitations of the study. GUM clinic attendees may differ from people at risk of HIV in the general population in terms of sociobehavioural characteristics and sexual risk behaviour. Recruiting clinic attendees restricts the sample to an at-risk population of individuals who use these services, and is likely to overestimate the prevalence of sexual risk behaviour and sexual health problems with respect to all MSM and black African men and women in the UK. Furthermore, causality cannot be inferred using cross-sectional design as a result of problems associated with temporality. Finally, the AURAH study did not measure markers of compulsive personality traits or childhood sexual abuse or intimate partner violence. The potential confounding or mediating effects of these factors cannot be investigated.

This preliminary work among MSM suggests the need to consider an integrated sexual health approach. Screening for depressive symptoms using brief instruments may be useful in identifying individuals who could be offered referral for potential interventions. At the same time, integration of substance use services or referral to services could also be used to alleviate symptoms and potentially reduce future sexual risk-taking and, alongside biomedical intervention, reduce HIV transmission.

The AURAH study research protocol and all versions of the study documents (information sheet, consent form and questionnaire) were approved by the North West London REC 2 research ethics committee (reference number 10/H0720/70). Instruments, protocols, tools and consent information for the AURAH study are available for download from the study website (www.astra-study.org).

Sexual risk behaviour in people enrolled in the START (Strategic Timing of Antiretroviral Therapy) trial

This section describes a substudy of the START trial. The START trial is an open-label, multicentre, international randomised trial comparing serious acquired immunodeficiency syndrome (AIDS) and non-AIDS morbidity or mortality between two management strategies for ART-naive individuals with baseline CD4 cell counts of > 500 cells/μl who are randomised to begin ART immediately (early ART) or to defer ART until the CD4 cell count declines to < 350 cells/μl or AIDS occurs (deferred ART). Accrual for the START trial was completed on 23 December 2013 with 4688 study participants enrolled from 215 sites in 35 countries. As part of the CAPRA programme of work, a substudy aimed to describe the baseline self-reported recent transmission risk behaviours and to assess sociodemographic, ethnic, lifestyle and other factors associated with these in START trial participants in order to examine the risk profile of these individuals (see Rodger *et al.*[52]).

The baseline and follow-up schedule for data collection was the same in both arms. HIV transmission risk behaviour assessment was conducted at baseline, at month 4 and every 12 months after randomisation. Sexual activity (vaginal or anal sex) during the previous 2 months was ascertained for (1) men having sex with women, (2) MSM and (3) women having sex with men. There were questions on the number of partners, type of partners (long term or other) and CLS with one or more serodifferent partners (CLS-D). For those participants who reported CLS-D in the past 2 months, there was a detailed inquiry on number and type of partners, frequency of sex and type of sex (receptive or insertive, vaginal or anal sex and whether or not ejaculation occurred).[18]

Human immunodeficiency virus transmission risk behaviour was also assessed, including recreational drug use. Information was collected on HIV transmission risk beliefs: each person was asked to tick which one of the following options was true: 'a person using HIV treatment who has an undetectable VL cannot/is much less likely to/is a little less likely/is just as likely/is more likely to pass on (transmit) HIV to someone else than someone not on treatment'.

The primary 'outcome' of interest was CLS-D. A key secondary outcome was CLS-D when the participant is the insertive partner in anal sex. Further secondary outcomes included all CLS and insertive sex with ejaculation.

Overall, 4499 participants were included in this baseline analysis; their median age was 36 years [interquartile range (IQR) 29–44 years, range 18–81 years]. The majority were of white ethnicity ($n = 2052$, 45%). Of the others, 31% were of black ethnicity, 13% were of Hispanic ethnicity and 8% were of Asian ethnicity. One-third ($n = 1518$, 33%) were recruited from Europe or Israel, and one-quarter ($n = 1132$, 25%) from South and Central America. The majority had been diagnosed with HIV within the previous 2 years ($n = 3028$, 66%), with 18% diagnosed less than 3 months before randomisation. As per eligibility criteria, all had CD4 cell counts of > 500 cells/μl, with 37% ($n = 1714$) having a CD4 cell count of > 700 cells/μl. All had a detectable HIV VL.

Overall, 17% (766/4600) of participants had CLS-D in the 2 months previously. MSM were more likely to report CLS-D ($n = 502$, 20%) than heterosexual men ($n = 72$, 9.2%) or heterosexual women ($n = 171$, 14%). Among those reporting CLS-D, MSM were also more likely than heterosexual men or women to have had more than one CLS-D partner, 39% (182/766) of MSM reported more than one CLS-D partner in the previous 2 months, compared with 19.4% ($n = 58$) of heterosexual men and 14% ($n = 147$) of heterosexual women. Of the MSM reporting CLS-D with at least one partner in the previous 2 months, 39% were the insertive partner with ejaculation on at least one occasion, whereas 48% reported being insertive with no ejaculation and 75% reported being the receptive partner on at least one occasion.

A substantial minority of people enrolled in the START trial reported CLS with discordant partners. The proportion reporting CLS-D is higher among MSM than among heterosexuals. A substantial proportion of MSM reporting CLS-D nevertheless appear to take measures to limit transmission risk. Reported CLS-D is less common in Europe and Asia, and in those of white or Asian ethnicity. This could reflect differences in being prepared to report such activity as well as real differences. Knowledge of the effects of ART on transmission risk is extremely low, particularly in heterosexual men and women.

Prior to the initiation of the START study at each clinical research site, the protocol, all informed consent forms and the participant information materials were submitted to, and approved by, the site's institutional review board or institutional ethics committee. A comprehensive protocol of the START trial can be accessed (it is of note that this document does not specifically describe the substudy investigated in this programme of work that is described above; however, a selection of participants for enrolment in the START trial is described on p. 19).[53]

The Partners of People on ART: a new Evaluation of the Risks (PARTNER) study

This section describes the PARTNER study, an observational multicentre longitudinal study of HIV-serodifferent heterosexual and MSM couples, in which the HIV-positive partner is on ART. The primary aim of this study is to estimate the risk of HIV transmission in serodifferent partners who have penetrative sex without using condoms, in which the positive partner is on ART with a plasma HIV-1 ribonucleic acid (RNA) load of < 200 copies/ml.

The need for this study was driven by the fact that, although it is well documented that treatment reduces the risk of HIV transmission, data describing how low the risk actually is, especially the risk associated with anal sex (gay or straight), are scarce (see Rodger *et al.*[54]). In fact, the limited information available when designing this study was mainly from studies of heterosexual couples: only 2% of participants (37 couples) in the HIV Prevention Treatment Network (HPTN) 052 study were MSM.[5] In addition, many of the participants in these studies, including the participants of the HPTN 052 study, said that they regularly used condoms. None of the previous observational studies restricted their analysis to people who reported not using condoms consistently, and, in the HPTN 052 study, 96% of the participants reported regular condom use.[5] In MSM, anal intercourse without a condom is the major risk factor for HIV acquisition, especially for the receptive partner. Currently, only two studies are looking at HIV transmission risk in MSM/anal sex: the PARTNER study, covering Europe, and Opposites Attract, co-ordinated from Australia.[55]

Serodifferent couples were eligible to take part if the HIV-positive partner was aged > 18 years and expected to remain on ART, and if the partners reported penetrative sex without using condoms in the month before enrolment (in this period the HIV-negative partner was aware of the HIV-positive status of the partner) and expected to have sex together again in the following months.

Both partners were asked for agreement to take part and signed separate informed consents. Data were collected after consent at baseline and then every 4–6 months. The information collected included sociodemographics, adherence to ART, sexual activity, frequency of intercourse, type of intercourse and whether or not ejaculation occurred, STIs and presence of symptoms suggestive of STIs, use of pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis, and injection drug use and sharing of needles, syringes or any part of injection equipment.

Human immunodeficiency virus-negative participants were also asked if they had CLS with anyone other than their HIV-positive partner since their last visit, the number of other partners and if any were HIV positive or of unknown serostatus. They were asked to test for a HIV infection every 6–12 months, in order to detect any serconversions that occurred. For the HIV-positive partner, the information on ART, CD4 cell counts and plasma HIV-1 RNA load were collected through a clinical case report form. Plasma HIV-1 RNA was measured in the HIV-positive partner according to routine care every 6–12 months. If the HIV-negative partner tested HIV positive, venous blood samples in ethylenediaminetetraacetic acid (EDTA) were taken from both partners to determine genetic relatedness of HIV-1 *pol* and *env* sequences; or, in other words, whether or not the transmission was linked.

Follow-up was stopped if the partnership ended, the partners moved away or either person in the partnership withdrew consent, but not if there were changes in sexual behaviour or use of ART (although such changes could lead to the follow-up time not being eligible for the main analysis).

The study recruited participants from 75 clinical sites in 14 European countries from September 2010. Follow-up in heterosexual couples ended on 31 May 2014, while recruitment and follow-up remains ongoing for MSM couples (PARTNER 2 trial) (see Rodger *et al.*[56]). Interim results were presented at the

Conference for Retroviruses and Opportunistic Infections in March 2014 and were published in the *Journal of the American Medical Association* in July 2016.[57]

The PARTNER study (phase 1) enrolled 1166 couples, of which 1004 had received at least one follow-up visit by the censoring date (31 May 2014). Overall, 888 couples contributed 1238 eligible couple-years of follow-up (CYFU), which means follow-up during which the HIV-positive partner had an undetectable VL on the most recent test (at most, 12 months before). The dropout rate among these couples was 11 per 100 CYFU. Of the 888 couples, 340 were MSM, 269 were heterosexual in which the male partner was HIV positive (male positive/female negative) and 279 were heterosexual in which the female partner was HIV positive (male negative/female positive). Couples contributed for a median 1.3 years (IQR 0.8–2.0 years) of eligible CYFU.

The median age was 40–45 years in HIV-negative and -positive MSM and heterosexuals. HIV-negative MSM reported CLS with their HIV-positive partner for a median 1.4 years (IQR 0.5–3.5 years) before enrolment, male-negative/female-positive couples for 2.8 years (IQR 0.6–7.5 years) and male-positive/female-negative couples for 3.6 years (IQR 0.7–11.4 years). Among heterosexual couples, almost all couples (99%) had vaginal sex with or without ejaculation, and 11.1% had anal sex. Among HIV-negative MSM, 67% of negative partners reported receptive anal sex without ejaculation, 45% reported receptive anal sex with ejaculation inside and 92% reported insertive anal sex.

Eleven HIV seroconversions occurred during eligible CYFU, but none was phylogenetically linked to the HIV-positive partner enrolled in the PARTNER study. This means that all these HIV infections were acquired from a different partner. Of the seroconverters, 10 were MSM and one was heterosexual. Given that zero linked transmission was observed, the estimated rate of HIV transmission from a positive partner with a plasma HIV-1 RNA load of < 200 copies/ml is zero. However, the upper limit of the 95% confidence interval is 0.3 per 100 CYFU, corresponding to an estimated upper limit of a 10-year risk of 3%.

When we distinguish between the different types of couples and types of sexual acts, the upper confidence limit for the rate of transmission for receptive anal sex without ejaculation is 8.14 and 1.68 per 100 CYFU for heterosexual women and MSM couples, respectively. The differences in the upper 95% confidence limits for the different type of couples and sexual practices reflect the different length of CYFU available. The fewer follow-up data available, the more uncertainty we have.

The PARTNER study has accrued, so far, more data on the risk of HIV transmission by anal sex (straight or gay) when the positive partner has an undetectable VL than any other study. However, these upper 95% confidence limits suggest that we cannot exclude appreciable levels of risk, especially for anal sex, and this is the reason why the recruitment and follow-up of MSM continues.

In the UK, the PARTNER study was reviewed and approved by the North West London REC 2 Ethics Committee (EC reference number 10/H0720/55). Ethics approval was obtained in-country for all other European sites involved in the study. Instruments, protocols, tools and consent information for the PARTNER study are available for download from the study website (www.chip.dk/PARTNER).

Modelling of the clinical effectiveness and cost-effectiveness of increased human immunodeficiency virus testing and immediate antiretroviral therapy at diagnosis in men who have sex with men in the UK

This final section describes the results of modelling analyses that take into account the information generated in studies done in the programme, as well as building on the research from published cohort studies and other studies over the past 20 years. The work was reported in two papers.[1,14] The first concentrated on understanding influences on the epidemic up to 2012 and described the structure and calibration of the model of HIV transmission, progression and the effect of ART that was developed for this. The model was then used to help us understand the relative influences of sexual risk behaviour change, rates of HIV testing and ART-induced virological suppression on HIV infection incidence up to 2012.[1] In the second paper we used the model to project future HIV infection incidence and other outcomes over the next 20 years, along with an economic analysis.[14]

In the model we reconstruct sexual risk behaviour, HIV transmission, progression and the effect of ART for the population of MSM in the UK from 1980 to 2010 using an individual-based stochastic computer simulation model, which captures the key underlying mechanisms that determine these processes (model adapted from that used in Phillips *et al.*,[58] itself developed from earlier versions[59–61]). We were able to calibrate the model quite closely to a range of data.

The model suggested that, after an initial period of high HIV infection incidence in the early 1980s, incidence declined in response to a decline in CLS. However, after the introduction of effective ART, the model suggests that there was an increase in CLS, associated with a rise in HIV infection incidence. Our analysis suggested that use of treatment, even under a policy of ART initiation only when the CD4 cell count was < 350 cells/μl^3, and in the context of a relatively low rate of HIV diagnosis, has had an appreciable impact on HIV infection incidence in the UK, resulting in most (82%) new infections being from people who are yet to be diagnosed. We estimated that incidence would have been 68% higher than that actually observed had ART not been introduced (but sexual risk behaviour changes remaining unchanged) and more than five times higher than the observed had condom use ceased.

Our study helped to explain the observed increase in HIV infection incidence in MSM epidemics over a period in which ART coverage and viral suppression has been increasing. Our analysis suggests it is the counter-effect of concomitant increases in CLS among MSM as a whole that has resulted in a net increase in incidence; the model outputs were not consistent with the data unless we assumed such a rise.

An implication of our finding was that extension of ART coverage, by increasing rates of diagnosis and with initiation of ART at higher CD4 cell counts, was likely to have an appreciable effect on reducing HIV infection incidence in MSM epidemics, so long as this does not also result in increases in CLS. A major public health implication of our work is the need to promote frequent HIV testing and to offer ART for the purposes of reduction in infectivity. A second important message is the fact that promotion of condom use

remains a critically important and effective element of prevention policies as it is acting to prevent more dramatic increases in HIV infection incidence.

The analysis was useful for understanding the influences on the epidemic, but in order to assess cost-effectiveness of different policy options it was necessary to project forward in time. We did this in a follow-on modelling exercise conducted in the last year of the research programme, and used the same model as that described above. For projecting forward, we assumed that levels of CLS and rates of testing would remain as they were in 2012.

Having reconstructed the epidemic to date, we projected outcomes to 2030, first assuming that there was no change in HIV testing patterns or in the initiation criteria for ART (CD4 cell count of 350/μl). We then considered outcomes under scenarios in which, from 2015, rates of testing were increased.

We found that for increased testing and earlier ART use to lead to a HIV infection incidence of < 1 per 1000 person-years, an increase in the overall proportion of MSM living with HIV who are virally suppressed on ART from the current level of 60% at present to 90% is needed, without any concomitant increases in CLS. A decline in incidence to around this level is required for us to see a reduction in the number of MSM living with a HIV infection. We argued that achieving such high levels of viral suppression is likely to require a cultural change in the approach to HIV testing, such that around 90% of men with HIV are diagnosed within 1 year of infection, together with initiation of ART at diagnosis. Interestingly, we find that increases in testing alone would have a substantial impact on incidence, at least as much or more than the effect of initiation of ART at diagnosis alone. Considering the potentially lower costs of ART associated with use of generic antiretrovirals, we found that there was scope for spending substantial funds in expanding HIV testing, which might include widespread free self-testing, greater testing outreach, simplified testing at clinics combined with regular telephone texting recall, improved partner notification and testing, and promotion of greater awareness of symptoms of primary HIV infection. It has been reported that online advertising campaigns directly lead to an increased uptake of requests for use of free self-sampling kits. If substantial increases in testing were achieved, our results suggest incidence should drop fairly rapidly as a result, potentially allowing the impact to be seen over a short time span, and it is of note that in 2015 the new NHS England policy was to provide ART to people with CD4 cell counts of > 350 cells/μl if this was needed to prevent transmission.[62]

Our findings point to the need for future research into means of greatly increasing the frequency with which men test for HIV. Self-testing may play an important role here, and we are investigating this in ongoing research. Modelling of the impact of introduction of PrEP is also important, with its potential impact on levels of CLS and HIV testing.

In conclusion, we found that substantial investment in increasing HIV testing uptake and frequency in MSM is likely to be a highly cost-effective means of reducing HIV infection incidence. However, it is important that levels of risky CLS do not increase, and that ART retention and adherence remain at a high level.

Strengths and limitations of the programme

Through the programme of work described in this report, it appears that the policy of initiating ART in all people diagnosed with a HIV infection, including those with a high CD4 cell counts, is likely to be cost-effective. Now that we have evidence from the main START trial that immediate ART initiation is beneficial to health, even in those with high CD4 cell counts, and there remains no evidence that ART initiation leads to an increase in CLS for which there is a transmission risk (the reverse is, in fact, the case), it has become clear that initiating ART in all MSM diagnosed with a HIV infection, including those with a high CD4 cell counts, could be adopted by the NHS.

This programme of research has also been of general benefit in giving us a greater depth of understanding of circumstances and other personal factors in HIV-positive populations as well as HIV-negative at-risk populations. Sexual behaviour and attitudes towards condom use and HIV have been a major focus, but sociodemographic circumstances and lifestyle factors, as well as mental and physical health and well-being, have provided important insights and will continue to be useful as a result of the ASTRA, CIPHER and AURAH studies all having ongoing, prospective dimensions to them. Furthermore, the PARTNER study has provided critical information on understanding HIV transmission risks, particularly through anal sex between men.

There are a number of strengths in our programme of work, including the recruitment of many thousands of people and the innovative modelling techniques that enabled us to address our key question. This has involved a tremendous collaborative effort from the many contributing investigators who represent a critical part of our programme strength. The collaborative approach by the whole research group enabled community involvement in the science and the research. Community participation was integrated, encouraged and supported in all aspects of this research. This included participation in the planning and design of studies, through enrolment and ongoing recruitment, analysis of the results for conference presentations and publications, and in the wider dissemination of the results and their implications. This process itself helped community advocates raise the profile of the research within our communities and try to ensure that the final results were widely shared.

Weaknesses are less apparent as we have fulfilled the objectives that we originally set ourselves. In terms of the ASTRA study cross-sectional analyses and the AURAH study, one limitation of the cross-sectional design is the difficulty in being assured of the direction of associations between factors and, therefore, any inferences about causality can only be made cautiously. Furthermore, all studies recruited at a somewhat lower rate than had originally been intended, but in no case has this had a serious impact. We modified the programme during its course in order to carry out a study in HIV-negative people in place of a second round of the ASTRA study in HIV-positive people, and this was, we feel, an appropriate adjustment to make mid-programme. We also note that although any full cost-effectiveness analysis involves some extrapolation through modelling, there are intrinsic limitations of this approach as a result of the need to make some assumptions beyond the available data. In addition, we took a relatively short time horizon for our economic evaluation and in future work we intend to increase this to $\geq$ 50 years. If we had to start the programme again, there is relatively little we would change apart from implementing the lessons that we learned during the programme about recruiting and retaining people, and in co-ordinating multiple sites.

We consider that we have addressed an important set of research questions about providing ART to all people with diagnosed HIV and, in doing so, this work could impact future HIV infection incidence in the UK and beyond.

Lessons learned

Lessons learned from the programme as a whole are that, although we recognise that our proposed programme of work was extremely ambitious, it was possible to perform an extensive and diverse programme of work around one key public health question and reach important conclusions. The willingness of the National Institute for Health Research (NIHR) to fund the PARTNER study when it was conducted across Europe and most funding went outside the UK was a critical positive element that has led to a global benefit. Lessons learned from our modelling are that a carefully conducted modelling exercise that attempts to closely calibrate a model to multiple different data sources on a process can be an extremely time-consuming process, but nevertheless important and worthwhile. Finally, other important lessons learned were that programmes of research need to be adaptable to reflect changes in research priorities as evidence emerges, and that funders recognise the merits of this as the NIHR did, and the need to maximise research outputs through linked funding (as was the case for the START substudy and the CIPHER study).

Recommendations for future research

Our cost-effectiveness analysis suggests that the answer to our specific question of whether or not a policy of ART initiation at diagnosis is likely to be cost-effective is yes, at least in MSM. Owing to the particularly high incidence in this group and the clear implications of early treatment to reduce transmission, all our modelling and cost-effectiveness work was ultimately focused on MSM, and so future work modelling the HIV epidemic in black Africans in the UK would be helpful to clarify which policy differences might be required in populations other than MSM.

The PARTNER study has proved a key resource for understanding HIV transmission risks. Further follow-up is required in PARTNER and other similar studies in order to reduce the potential for sampling error in our estimates. Furthermore, the ASTRA study has been highly useful in understanding the sexual behaviour and many other aspects of the HIV-diagnosed population in the UK. It will be important in the future to perform similar studies to understand how awareness, behaviours and experiences are changing over time in the evolving climate of HIV prevention and care. Likewise, in HIV-negative people, the AURAH study is providing a snapshot of behaviours of people attending sexual health clinics, and further studies in future to assess changes would be worthwhile. Ideally, both types of studies would be based on random sampling from a well-defined sampling frame, although this would probably make them considerably more costly undertakings than the studies we performed.

The future research agenda for 2016 onwards is clear – we need to find the means of providing an optimal HIV prevention environment with regard to HIV testing, CLS and PrEP, using resources as efficiently as possible, but bearing in mind that resources spent now could avert much higher costs in future years. Further developments in modelling HIV transmission in the UK will be of importance for continuing to make sound public health decisions based on cost-effectiveness considerations.

Implications for practice

Key outstanding issues for prevention of new infections that emerge from our modelling work are (1) that HIV testing rates in those having CLS should be increased and (2) that efforts should continue to minimise risky CLS (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 HIV or PrEP to prevent HIV). PrEP was evaluated in UK settings in the light of recent positive findings from the PROUD and IPERGAY studies using the model calibrated as part of this programme, and found to be cost-effective.[63] On 10 April 2017, the decision was taken to make PrEP available on the NHS in Scotland.[64] PrEP is not currently available in England on the NHS; it is available only by private prescription from 56 Dean Street.[65] It is likely, however, that many men are ordering generic drugs online and, therefore, PrEP is already an important part of the HIV prevention landscape and clinical practice.

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START

A comprehensive list of all authors is cited in the main start papers[18,52,53] and in appendix D of the study protocol.

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Contributions of authors

All authors were involved in study conception and design, acquisition, interpretation or analysis of the data. All authors critically reviewed this report for important intellectual content.

Ada Miltz (PhD student) co-ordinated and led the writing of the final report.

Andrew N Phillips (Professor of Epidemiology and Biostatistics), **Andrew Speakman** (Research Associate), **Alison Rodger** (Senior Lecturer and Honorary Consultant in Infectious Diseases) and **Fiona C Lampe** (Senior Lecturer in Epidemiology and Medical Statistics) jointly played a key role in leading all the studies as core programme managers.

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Data sharing statement

We have a number of planned analyses for the AURAH and ASTRA studies, but welcome proposals for additional analysis; please contact Dr Fiona Lampe (f.lampe@ucl.ac.uk). The Study Steering Committee will review proposals for the time being. After which time, the data will be made freely available in anonymised form via the corresponding author.

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