Effect of pre-exposure prophylaxis and combination HIV prevention for men who have sex with men in the UK: a mathematical modelling study

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Summary

Background **HIV transmission in men who have sex with men (MSM) in the UK has shown no sign of decreasing in the past decade. Additional prevention measures are needed. We aimed to estimate the effect of various potential interventions implemented individually and in combination on prevention of HIV infection.**

Methods **We extended a deterministic partnership-based mathematical model for HIV transmission, informed by detailed behavioural and surveillance data, to assess the effect of seven different HIV interventions implemented in MSM (aged 15–64 years) in the UK during 2014–20, including increasing rates of HIV testing, test-and-treat programmes, pre-exposure prophylaxis (PrEP), and sexual behavioural changes. We did sensitivity analyses on risk compensation.**

Findings **We predicted a baseline of 16 955 new infections (IQR 13 156–21 669) in MSM in the UK during 2014–20. At a coverage of ≤50%, testing twice a year outperformed all other interventions. Of all intervention combinations, only the combined effect of test and treat and annual HIV testing (61·8%, IQR 47·2–81·8, of total incidence) was greater than the sum of effects of the two interventions individually (32·6%, 23·7–46·0, and 23·9%, 16·5–33·3, respectively). Simultaneous PrEP, expansion of HIV testing, and initiation of test-and-treat programme in 25% of high-activity MSM could save 7399 (IQR 5587–9813) UK MSM from HIV infection (43·6%, IQR 32·9–57·9, of total incidence). An increase in unsafe sex or sexual partners to 50% or more could substantially reduce the effect of interventions, but is unlikely to negate the prevention benefit completely.**

Interpretation **PrEP could prevent a large number of new HIV infections if other key strategies including HIV testing and treatment are simultaneously expanded and improved. Without PrEP, HIV incidence in MSM in the UK is unlikely to decrease substantially by the end of this decade.**

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Introduction

In the UK, an estimated 103 700 people were living with HIV in 2014, around 43% of whom were men who have sex with men (MSM), which was equivalent to 4·9% prevalence in MSM aged 15–44 years.[1] On the basis of estimates from a CD4 back-calculation model,[2] about 2600 MSM in England and Wales have been infected with HIV every year in the past 10 years, with a slight increase to 2800 in 2014, and without alternative prevention measures incidence is expected to remain at this level throughout the decade.[3]

Attempts to prevent HIV transmission in the UK have focused on promotion of proper and consistent condom use and increasing coverage and frequency of HIV testing.[1] But because these interventions alone have been insufficient to reduce HIV incidence in UK MSM over time, more attention has been paid to alternative strategies of HIV infection control, including use of pre-exposure prophylaxis (PrEP). Two PrEP trials—the PROUD study in England[4] and the IPERGAY study in France and Canada[5]—had to discontinue the placebo group and provide PrEP to all eligible participants after their interim results showed the high protective effect of PrEP.

Because the combination of conventional and alternative prevention measures is now being considered, an increased understanding is needed of their potential effect on HIV transmission in MSM in the UK. We did this mathematical modelling study to assess the potential effect of various HIV prevention interventions, both individually and in combination, on HIV transmission during 2014–20. We also investigated the sensitivity of our results to variation in intervention coverage, PrEP effectiveness, and the effects of potential risk compensation.

Methods

Modelling and data sources

For our mathematical modelling analysis, we extended a previous deterministic partnership-based model for HIV transmission in MSM aged 15–64 years in the UK.[3] We used the R software package (version 2.15.3)[6] for model building and analysis. The model time step was 1 day. The model consisted of 15 compartments (appendix, p 28).

See Online for appendix

Research in context

Evidence before this study

We searched PubMed for studies published in English up to Nov 30, 2015, with the search terms "HIV", "intervention" or "prevention", "men who have sex with men" or "MSM" or "homosexual" or "gay", and "model". We identified five studies that used a mathematical model to estimate the potential effect of combinations of HIV interventions in men who have sex with men (MSM) in China, South Africa, South Korea, the UK, and the USA. Four studies assessed the effect of increasing HIV testing and early treatment but only three studies included pre-exposure prophylaxis (PrEP). PrEP showed a promising effect against HIV infection in MSM in many settings and seemed to be more effective than other included interventions. No studies assessed the effect of PrEP in MSM in the UK.

Added value of this study

We used a mathematical model to estimate the effect of seven different HIV interventions implemented individually and simultaneously in MSM in the UK during 2014–20. Most of the included interventions have not previously been assessed. The model incorporated many important heterogeneities and was calibrated and validated against multiple surveillance datasets and national estimates. Our findings show that PrEP can be highly effective against HIV transmission at the population level and could outperform other interventions at the same level of programme coverage.

Implications of all the available evidence

A feasible combination of PrEP, test-and-treat strategies, and HIV testing programmes implemented in small groups of MSM could prevent a substantial number of new infections, even with a high level of risk compensation. Future work may investigate the effect of changes in other behavioural factors on the result of interventions.

The five disease stages (primary HIV infection; and CD4 counts of 500 cells per μL or higher, 350–499 and 200–349 cells per μL, and less than 200 cells per μL) had different HIV transmission probabilities derived from the average viral load in each stage. Once individuals progressed to the treatment stage, they remained there until being removed from the model because of mortality or age older than 64 years.

MSM were divided into current and past MSM. Current MSM reported having sex with men in the past 5 years and were assumed to continue to have new male sexual partners. Past MSM reported having no sex with men in the past 5 years and were assumed in our model no longer to have sex with men. We used this categorisation to exclude individuals who might have no contribution towards further HIV transmission in MSM. Men were further divided into those with low sexual activity, defined as MSM with, on average, one or fewer new male sexual partners per year, and those with high sexual activity, defined as MSM with more than one new sexual partner a year. We assumed that MSM did not change activity level except after diagnosis with HIV. If diagnosed, 66% of high-activity MSM were assumed to become low activity and 7% of low-activity MSM were assumed to become high activity, as derived from a cohort study in UK MSM.[7] Model MSM were categorised into two age groups: 15–34 years (group 1) and 35–64 years (group 2). We assumed that the sizes of the two age groups changed over time in line with the general UK male population. The initial model population size in 2000 was 648 500 MSM, 259 500 of whom were aged 15–34 years and 389 000 aged 35–64 years.[3]

The model simulated two types of sexual partnerships: one-off partnerships and repeat partnerships. One-off sexual partnership consists of a single sex act, whereas the repeat partnership lasts for a finite period of time and consists of more than one sex act with the same partner. We assumed non-random mixing between partners, with a method based on odds ratios,[8] and, in line with data, that MSM were more likely to select new sexual partners of the same age group, sexual activity level, and perceived HIV serostatus.[3] HIV can only be transmitted through five types of sex between men: protected and unprotected receptive anal intercourse, protected and unprotected insertive anal intercourse, and unprotected receptive oral intercourse. We describe further details of the model and the force of infection derivation elsewhere.[3]

The main sources for estimation of demographic and behavioural parameters were the 2000 National Survey of Sexual Attitudes and Lifestyles (NATSAL),[9] the 2000–06 Gay Men's Sexual Health Survey (GMSHS) in London,[10] and the 2000–08 London Gym Survey (GYM).[11] We adjusted data from the community-based convenience-sample GMSHS and GYM surveys to match key important variables from the national-based probability-sample NATSAL survey.[3] The national HIV/AIDS surveillance databases including HIV/AIDS diagnoses and CD4 surveillance provided data used extensively throughout parameterisation. We estimated unknown parameters through model fitting with the Monte Carlo filtering method.[12] We sampled 20 000 different combinations of the fitted parameters with Latin Hypercube sampling and ran 20 000 model simulations to match the 2001–09 estimates of the overall and undiagnosed HIV prevalence simultaneously. 1093 parameter sets fitted to the data and were used to simulate the HIV epidemic in MSM in the UK from 2001 to 2020. We then did model validation by comparing the model estimates to the national estimates of annual new HIV infections, the number of new HIV diagnoses, and the number of ART-treated MSM during 2001–09.[3]

HIV interventions

Model simulations were done for the period 2001–20 and intervention programmes were introduced in 2014. We assessed the effect of interventions with the number of HIV infections prevented during the intervention period compared with the existing scenario in which no additional interventions have been implemented. We additionally assessed the changes over time in the number of new infections and the number of individuals living with HIV. The model outputs are presented as median estimates with IQRs.

Findings from our previous study[3] suggested that undiagnosed HIV, repeat sexual partnerships, and young and high-activity MSM were the most important drivers of the HIV epidemic in UK MSM. Several interventions have been proposed in modelling studies[13] and have garnered interest.[14,15] We consequently formed and investigated seven individual HIV interventions: (1.1) test for HIV once a year; (1.2) test for HIV twice a year; (1.3) a test-and-treat programme assuming the ART initiation rate of those with CD4 count of less than 350 cells per μL to all diagnosed MSM regardless of CD4 count; (1.4) PrEP; (1.5) reducing the number of repeat sexual partners by 0·5 times; (1.6) reducing the number of one-off sexual partners by 0·5 times; and (1.7) reducing unprotected anal intercourse with repeat sexual partners by 0·5 times. The appendix summarises key parameters and details for modelling of the individual interventions.[3,16] Each intervention was implemented in three target groups: all MSM, MSM aged 15–34 years, and high-activity MSM. The intervention coverage, which we defined as the proportion of MSM who adopted each intervention, was assumed to be 100% for clarity of exposition in all scenarios of individual and combined interventions, and should be considered as the maximum effect of the intervention because this coverage is highly unlikely. We also assessed the effects of reducing the coverage of the individual interventions to 75%, 50%, and 25%. We also analysed changes to PrEP coverage in conjunction with changes to PrEP effectiveness from 44% to 20%, 60%, 80%, and 100% to show the joint effects these two parameters have on incidence reduction.

We modelled the seven combinations of the individual interventions: (2.1) test once a year and decrease unprotected anal intercourse with repeat sexual partners, (2.2) reduce the number of repeat sexual partners and decrease unprotected anal intercourse with repeat sexual partners, (2.3) test once a year and test and treat, (2.4) PrEP and test and treat, (2.5) PrEP and decrease unprotected anal intercourse with repeat sexual partners, (2.6) PrEP and reduce the number of repeat sexual partners, and (2.7) all individual interventions except test once a year. The combined interventions are applied only to all MSM. All parameter values in individual intervention scenarios remained unchanged in the combined intervention scenarios.

We then assessed the effect of various combinations of selected interventions at more realistic levels of coverage. We used the results from the previous intervention analyses to inform several practical scenarios of implementation of various interventions simultaneously on the basis of more conservative coverage assumptions. We mainly focused on the interventions that performed well individually or in combination with specific interventions. We assumed that all interventions achieved 25% coverage of the target populations. We used the extreme risk-compensation assumption to represent a near worst-case scenario.

Sensitivity analysis

We explored the effects of risk compensation—having more sexual partners, increasing unsafe sex, and with less HIV testing—resulting from implementation of the individual interventions. In the target groups of interventions, we specifically increased the repeat sexual partner change rates and the proportion of MSM who have unprotected anal intercourse with repeat sexual partners as well as decreasing the HIV diagnosis rates, all by 25%, 50%, 75%, and 100%. The sensitivity

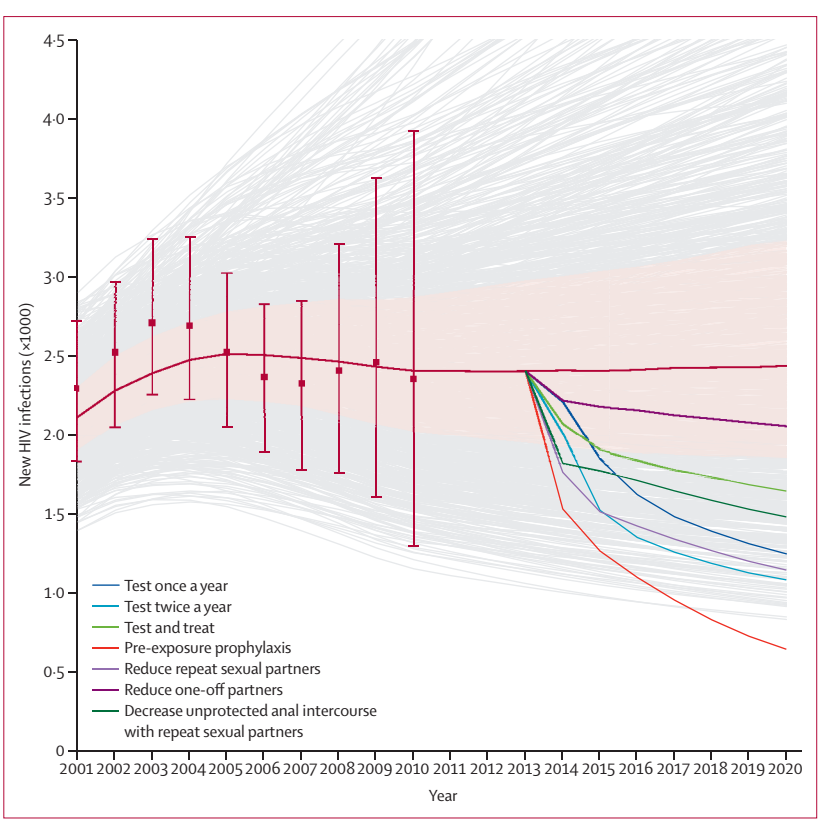

Figure 1: **Estimated numbers of new HIV infections between 2001 and 2020 in the status quo and the maximum effect of individual intervention scenarios at 100% coverage**

Light grey lines show estimates from 1093 simulations in the status-quo scenario. The dark red line shows median estimates with IQRs (light red lines) from these simulations. Dots and error bars show national estimates in England and Wales during 2001–10.[2] The average goodness-of-fit of the model is 94·4%. The coloured lines depict the median estimates of new HIV infections during 2014–20 in the seven individual intervention scenarios with 100% coverage.

	Number of participants*	Number of infections prevented†	Proportion of infections prevented (%)‡	Total infections	Unit effect§	New infections in 2020	HIV incidence in 2020 (%)	Number living with HIV in 2020	HIV prevalence in 2020 (%)
Status quo	..	..	..	16 955 (13 156–21 669)	..	2435 (1854–3226)	0·34 (0·26–0·45)	52 268 (45 982–59 794)	7·26 (6·37–8·30)
Individual interventions									
(1.1) Test once a year									
All MSM	772 600	5522 (4021–7807)	32·6 (23·7–46·0)	11 090 (8440–14 400)	0·007	1245 (907–1678)	0·17 (0·13–0·23)	46 525 (41 501–52 804)	6·45 (5·76–7·33)
MSM aged 15–34 years	366 400	3547 (2488–5273)	20·9 (14·7–31·1)	13 136 (10 148–16 783)	0·010	1629 (1213–2131)	0·23 (0·17–0·30)	48 549 (42 982–55 148)	6·74 (5·96–7·65)
High-activity MSM	299 200	5090 (3730–7258)	30·0 (22·0–42·8)	11 518 (8831–14 886)	0·017	1334 (976–1777)	0·18 (0·14–0·25)	46 869 (41 821–53 262)	6·51 (5·81–7·40)
(1.2) Test twice a year									
All MSM	772 600	7089 (5247–9848)	41·8 (30·9–58·1)	9521 (7197–12 358)	0·009	1081 (782–1425)	0·15 (0·11–0·20)	45 074 (40 439–50 917)	6·25 (5·61–7·07)
MSM aged 15–34 years	366 400	4651 (3374–6746)	27·4 (19·9–39·8)	11 999 (9242–15 286)	0·013	1477 (1096–1914)	0·21 (0·15–0·27)	47 398 (42 116–53 809)	6·58 (5·85–7·47)
High-activity MSM	299 200	6653 (4883–9198)	39·2 (28·8–54·2)	9991 (7633–12 937)	0·022	1145 (849–1524)	0·16 (0·12–0·21)	45 531 (40 877–51 423)	6·32 (5·67–7·13)
(1.3) Test and treat									
All MSM	12 600	4053 (2790–5654)	23·9 (16·5–33·3)	12 640 (9960–16 036)	0·322	1642 (1268–2133)	0·23 (0·18–0·30)	48 087 (42 851–53 963)	6·68 (5·95–7·49)
MSM aged 15–34 years	4300	2579 (1708–3583)	15·2 (10·1–21·1)	14 229 (11 177–18 117)	0·600	1918 (1477–2500)	0·27 (0·21–0·35)	49 650 (44 192–56 028)	6·89 (6·13–7·78)
High-activity MSM	7100	2937 (1951–4210)	17·3 (11·5–24·8)	13 834 (10 869–17 476)	0·414	1853 (1413–2385)	0·26 (0·20–0·33)	49 353 (43 887–55 444)	6·85 (6·09–7·70)
(1.4) PrEP									
All MSM	537 800	9955 (7402–12 872)	58·7 (43·7–75·9)	7036 (5566–8775)	0·019	642 (504–803)	0·09 (0·07–0·11)	42 980 (38 757–47 726)	5·97 (5·38–6·63)
MSM aged 15–34 years	331 100	7053 (5175–9226)	41·6 (30·5–54·4)	9938 (7846–12 459)	0·021	1036 (803–1311)	0·14 (0·11–0·18)	45 408 (40 817–50 909)	6·33 (5·68–7·09)
High-activity MSM	294 100	8665 (6513–11 336)	51·1 (38·4–66·9)	8272 (6581–10 292)	0·029	819 (637–1023)	0·11 (0·09–0·14)	44 134 (39 677–49 168)	6·15 (5·52–6·85)
(1.5) Reduce number of repeat sexual partners									
All MSM	558 900	7263 (5565–9424)	42·8 (32·8–55·6)	9637 (7612–12 277)	0·013	1143 (884–1489)	0·16 (0·12–0·21)	45 454 (40 720–51 150)	6·32 (5·67–7·12)
MSM aged 15–34 years	338 300	5005 (3671–6642)	29·5 (21·7–39·2)	11 903 (9401–15 084)	0·015	1519 (1168–1971)	0·21 (0·16–0·27)	47 269 (42 293–53 517)	6·59 (5·89–7·46)
High-activity MSM	304 300	5513 (4080–7314)	32·5 (24·1–43·1)	11 426 (8975–14 318)	0·018	1436 (1099–1831)	0·20 (0·15–0·25)	47 045 (41 996–53 100)	6·53 (5·84–7·38)

(Table 1 continues on next page)

analysis on risk compensation was done only on scenarios with 100% intervention coverage.

Role of the funding source

HIV specialists from the funder of this study were fully involved in the study as co-researchers. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The model estimates of the number of new HIV infections in UK MSM in the past decade showed good consistency with the national estimates (figure 1). The status-quo scenario estimated a total of 16 955 HIV infections in MSM in the UK, with around 2400 new infections annually during 2014–20 (table 1), which is equivalent to about 6·6 new HIV infections every day. Without additional interventions, 52 268 MSM are expected to be living with HIV in the UK by 2020, with an annual incidence of 0·34% (table 1).

With 100% programme coverage, PrEP prevented the greatest number of HIV infections (table 1). Even when targeted only at high-activity men, PrEP was more effective than all other individual interventions that targeted the entire UK MSM population (table 1, appendix p 32). A large number of MSM could also be protected from HIV infection by decreasing the number of repeat sexual partners by 0·5 times (table 1). Decreasing the proportion of men who had unprotected anal intercourse with repeat

	Number of participants*	Number of infections prevented†	Proportion of infections prevented (%)‡	Total infections	Unit effect§	New infections in 2020	HIV incidence in 2020 (%)	Number living with HIV in 2020	HIV prevalence in 2020 (%)
(Continued from previous page)									
(1.6) Reduce number of one-off sexual partners									
All MSM	558 900	1973 (1455–2706)	11·6 (8·6–16·0)	14 901 (11 585–18 961)	0·004	2055 (1558–2672)	0·29 (0·22–0·37)	50 530 (44 561–57 528)	7·02 (6·19–7·99)
MSM aged 15–34 years	338 300	1176 (856–1656)	6·9 (5·1–9·8)	15 732 (12 230–20 060)	0·003	2213 (1681–2873)	0·31 (0·23–0·40)	51 155 (45 156–58 279)	7·10 (6·27–8·10)
High-activity MSM	304 300	1922 (1416–2646)	11·3 (8·4–15·6)	14 951 (11 622–19 022)	0·006	2063 (1564–2683)	0·29 (0·22–0·37)	50 584 (44 595–57 578)	7·02 (6·19–8·00)
(1.7) Decrease unprotected anal intercourse with repeat sexual partners									
All MSM	558 900	5271 (3948–7114)	31·1 (23·3–42·0)	11 529 (8930–14 891)	0·009	1479 (1111–1955)	0·21 (0·15–0·27)	47 166 (41 987–53 395)	6·54 (5·82–7·42)
MSM aged 15–34 years	338 300	3481 (2561–4839)	20·5 (15·1–28·5)	13 306 (10 397–17 108)	0·010	1776 (1364–2346)	0·25 (0·19–0·33)	48 672 (43 229–55 408)	6·76 (6·00–7·69)
High-activity MSM	304 300	4134 (3011–5647)	24·4 (17·8–33·3)	12 691 (9898–16 292)	0·014	1672 (1267–2199)	0·23 (0·18–0·31)	48 273 (42 811–54 546)	6·69 (5·94–7·58)
Combined interventions									
(2.1) Test once a year and decrease unprotected anal intercourse with repeat sexual partners	1 331 500	8344 (6285–11 033)	49·2 (37·1–65·1)	8371 (6333–10 927)	0·006	902 (648–1220)	0·13 (0·09–0·17)	44 103 (39 470–49 512)	6·12 (5·48–6·88)
(2.2) Reduce number of repeat sexual partners and unprotected anal intercourse with repeat sexual partners	1 117 800	10 225 (7802–13 171)	60·3 (46·0–77·7)	6721 (5279–8530)	0·009	724 (554–937)	0·10 (0·08–0·13)	42 745 (38 473–47 564)	5·95 (5·35–6·62)
(2.3) Test once a year and test and treat	785 200	10 471 (7996–13 873)	61·8 (47·2–81·8)	6430 (5078–8005)	0·013	609 (468–768)	0·08 (0·06–0·11)	42 016 (37 973–46 511)	5·83 (5·27–6·46)
(2.4) PrEP and test and treat	550 400	11 803 (8842–15 324)	69·6 (52·2–90·4)	5137 (4139–6327)	0·021	403 (331–494)	0·06 (0·05–0·07)	41 033 (37 190–45 259)	5·70 (5·16–6·29)
(2.5) PrEP and decrease unprotected anal intercourse with repeat sexual partners	1 096 700	11 664 (8919–15 103)	68·8 (52·6–89·1)	5262 (4141–6656)	0·011	479 (370–610)	0·07 (0·05–0·08)	41 344 (37 402–45 613)	5·74 (5·19–6·33)
(2.6) PrEP and reduce number of repeat sexual partners	1 096 700	12 653 (9638–16 310)	74·6 (56·8–96·2)	4306 (3436–5325)	0·012	345 (274–424)	0·05 (0·04–0·06)	40 564 (36 705–44 633)	5·65 (5·11–6·22)
(2.7) All interventions except test once a year	2 999 700	16 368 (12 673–20 911)	96·5 (74·7–123·3)	626 (507–777)	0·005	15 (12–19)	<0·01 <0·01	36 375 (33 219–39 720)	5·07 (4·62–5·53)

Data are median (IQR), unless otherwise indicated. Estimates were derived from 1093 simulations. The status-quo scenario shows the estimates without any additional interventions. The combined interventions were only applied to all MSM. Coverage was assumed to be 100% for both individual and combined interventions. PrEP was provided only to HIV-negative current MSM. MSM=men who have sex with men. PrEP=pre-exposure prophylaxis. *The total number of participants covered by each intervention during the intervention period. For the combined interventions, this number is simply the sum of the coverage of the individual interventions. The number of test-and-treat participants represents only those who were treated with ART early in their disease course because of the programme. †Numbers were derived from the difference between the median estimates of infections in the status-quo scenario and the numbers of infections in the scenarios with interventions. ‡Percentages were calculated by dividing the median estimates of infections in the status-quo scenario by the number of infections prevented by the interventions. §Number of infections prevented per programme participant.

***Table 1*: Estimated maximum number of HIV infections prevented by the individual and combined interventions during 2014–20**

sexual partners by 0·5 times reduced incidence by almost a third during the intervention period (table 1).

An estimated 5522 new infections (32·6% of total incidence) would be prevented by testing annually at 100% coverage (table 1). Twice-yearly testing in all UK MSM increased the number of prevented infections to 7089, which is equivalent to a 41·8% reduction in incidence (table 1). Early provision of ART (test and treat) reduced total incidence by 23·9%; one test-and-treat participant could prevent 0·322 new infections during 2014–20, which is around 17 times higher than PrEP (unit effect 0·019; table 1).

Alteration of the coverage of interventions had a large effect on prevention of new infections (figure 2). Reducing repeat sexual partnerships was the most affected intervention, with a decrease of about 75% in effect as coverage reduced from 100% to 25%, whereas the same reduction in coverage resulted in a 55%

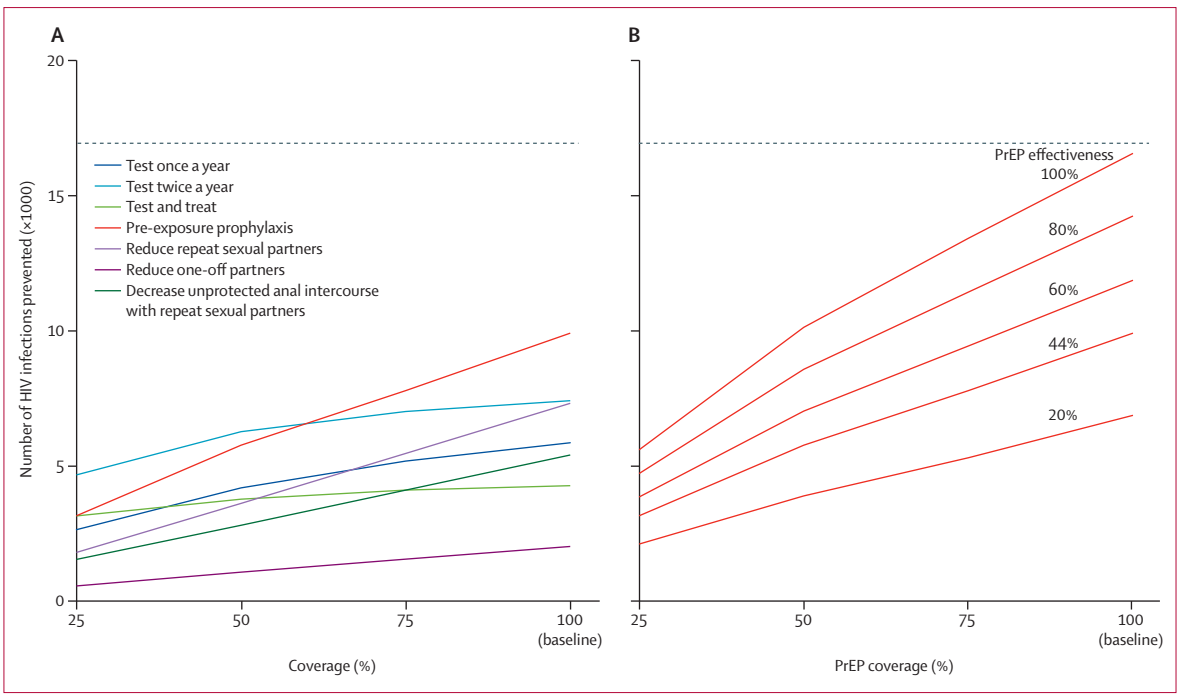

***Figure 2*: Median estimates of the total numbers of HIV infections prevented during 2014–20**
Estimates for varying intervention coverage (A) and PrEP coverage and effectiveness (B). Dashed line shows the median estimate of the total number of HIV infections in the status-quo scenario. For HIV testing programmes, coverage excluded men who had already been tested at least once a year in the status-quo scenario. For test and treat, the coverage is the proportion of men diagnosed with HIV at CD4 counts of 350 cells per μL or higher and excluded men who had already been treated in the status quo. PrEP=pre-exposure prophylaxis.

decrease in effect for testing once a year, and of 37% for testing twice a year (figure 2). The robustness to variation in programme coverage suggests that expansion of HIV testing and treatment might still be effective even when adopted by a smaller proportion of MSM. At 25% coverage of all interventions, testing twice a year produced the greatest effect; the effect of test-and-treat programmes was greater than for most other interventions and was on par with PrEP (figure 2). The other individual interventions tended to show a roughly linear association between coverage and effect (figure 2).

With an assumed effectiveness of 44%, if coverage was 50% rather than 100%, PrEP would fail to prevent 4144 new infections (figure 2). Increasing the effectiveness raised the number of infections prevented, irrespective of the coverage (figure 2). The PrEP intervention with 100% coverage and 20% effectiveness was able to prevent 1275 more cases than 25% coverage with 100% effectiveness (6893 cases *vs* 5618 cases). However, at low to moderate effectiveness (≤60%) but high coverage (≥75%), increasing PrEP coverage seemed to have a slightly greater effect than did increasing effectiveness (figure 2). On average, a 1% increase in PrEP coverage led to an increase of 1·90% in effect, whereas a 1% increase in PrEP effectiveness led to an increase of 1·25% (figure 2).

We recorded diminishing returns for most combined interventions. For example, programmes to increase frequency of HIV testing and decrease unprotected anal intercourse with repeat sexual partners were estimated to each prevent about a third of new infections when implemented separately at 100% coverage, whereas combining both programmes achieved only 49·2% incidence reduction (table 1). Only the combination of annual HIV testing with the test-and-treat programme was able to provide an incidence reduction greater than the sum of the effects of the two individually (appendix, p 36).

We investigated 12 practical scenarios (table 2). The first scenario (3.1) assumed that PrEP was provided to 25% of the high-activity HIV-negative MSM in the UK and, for high-activity men who did not use PrEP, 25% had an annual HIV test. This strategy prevented 26·4% of HIV infections, an effect that increased to 37·2% when PrEP coverage was increased to 50% (scenario 3.2). Addition of test and treat to scenario 3.1 prevented 7399 cases (43·6% of total incidence), the highest number among all the practical scenarios assessed (scenario 3.3). Scenario 3.3 also provided the largest unit effect (0·053). Replacement of test-and-treat strategies with programmes to encourage fewer sexual partners (scenario 3.4) and less unprotected anal intercourse (scenario 3.5) had a lower effect than the test-and-treat scenarios (appendix, p 40).

In the analysis of risk compensation in PrEP users, scenario 3.6 assumed that all PrEP men in scenario 3.1 completely stopped using condoms with repeat sexual partners. This assumption resulted in HIV incidence effect falling to 11·5% (table 2). Surprisingly, scenario 3.7,

which assumed that all PrEP men in scenario 3.1 acquired twice as many repeat sexual partners, increased incidence effect to 28·0% compared with scenario 3.1 (26·4%; table 2). This result was because more sexual partnerships in PrEP men would require a larger number of non-PrEP partners, including infected men, which

	Number of participants*	Number of infections prevented†	Proportion of infections prevented (%)‡	Total infections	Unit effect§	New infections in 2020	HIV incidence in 2020 (%)	Number with HIV in 2020	HIV prevalence in 2020 (%)
(3.1) PrEP and test once a year	137 400	4 480 (3326–6018)	26·4 (19·6–35·5)	12 363 (9680–15 830)	0·033	1466 (1117–1931)	0·20 (0·16–0·27)	47 879 (42 576–54 266)	6·66 (5·92–7·55)
PrEP in 25% of HIV-negative high-activity MSM	78 500	..	..	..	..	..	..	..	..
Test once a year in 25% of non-PrEP high-activity MSM	58 900	..	..	..	..	..	..	..	..
(3.2) More PrEP and test once a year	196 300	6302 (4739–8483)	37·2 (28·0–50·0)	10 564 (8306–13 409)	0·032	1154 (891–1494)	0·16 (0·12–0·21)	46 203 (41 246–52 048)	6·43 (5·74–7·25)
PrEP in 50% of HIV-negative high-activity MSM	157 000	..	..						..
Test once a year in 25% of non-PrEP high-activity MSM	39 300	..	..	..	..	..	..	..	..
(3.3) PrEP, test once a year, and test and treat	140 600	7399 (5587–9813)	43·6 (32·9–57·9)	9483 (7563–11 865)	0·053	958 (755–1216)	0·13 (0·11–0·17)	45 003 (40 351–50 395)	6·26 (5·62–7·02)
As in scenario 3.1	137 400	..	..	..	..	..	..	..	..
Added: test and treat in 25% of diagnosed MSM	3200	..	..	..	..	..	..	..	..
(3.4) PrEP, test once a year, and fewer repeat sexual partnerships	257 500	5743 (4339–7634)	33·9 (25·6–45·0)	11 137 (8730–14 223)	0·022	1270 (975–1672)	0·18 (0·14–0·23)	46 784 (41 688–52 846)	6·51 (5·80–7·36)
As in scenario 3.1	137 400	..	..	..	..	..	..	..	..
Added: reduce repeat sexual partnerships by 0·5 times in 25% of all non-PrEP MSM	120 100	..	..	..	..	..	..	..	..
(3.5) PrEP, test once a year, and less unprotected anal intercourse	257 500	5229 (3952–6999)	30·8 (23·3–41·3)	11 579 (9069–14 780)	0·020	1348 (1029–1770)	0·19 (0·14–0·25)	47 203 (41 955–53 422)	6·57 (5·83–7·44)
As in scenario 3.1	137 400	..	..	..	..	..	..	..	..
Added: reduce unprotected anal intercourse by 0·5 times in 25% of all non-PrEP MSM	120 100	..	..	..	..	..	..	..	..
(3.6) PrEP and test once a year but with (risk compensation) no condom use with repeat sexual partners	137 400	1950 (1195–3056)	11·5 (7·0–18·0)	14 836 (11 650–18 992)	0·014	1862 (1421–2454)	0·26 (0·20–0·34)	50 237 (44 401–57 316)	6·99 (6·17–7·98)
As in scenario 3.1	137 400	..	..	..	..	..	..	..	..
Added: (risk compensation) completely stop using condoms with repeat sexual partners in all PrEP MSM	..	..	..	..	..	..	..	..	..
(3.7) PrEP and test once a year but with (risk compensation) more repeat sexual partnerships	137 400	4750 (3582–6412)	28·0 (21·1–37·8)	12 065 (9455–15 432)	0·035	1411 (1082–1852)	0·20 (0·15–0·26)	47 561 (42 340–53 899)	6·62 (5·89–7·50)
As in scenario 3.1	137 400	..	..	..	..	..	..	..	..
Added: (risk compensation) increase repeat sexual partnerships by two times in all PrEP MSM	..	..	..	..	..	..	..	..	..
(3.8) PrEP and test once a year but with (risk compensation) no condom use with repeat sexual partners and (risk compensation) more repeat sexual partnerships	137 400	3782 (2796–5232)	22·3 (16·5–30·9)	13 009 (10 174–16 663)	0·028	1563 (1191–2056)	0·22 (0·17–0·29)	48 405 (43 008–55 019)	6·73 (5·98–7·65)
As in scenarios 3.6 and 3.7	137 400	..	..	..	..	..	..	..	..
(3.9) Reduce repeat sexual partnerships and test once a year	214 500	3761 (2811–5065)	22·2 (16·6–29·9)	13 054 (10 118–16 744)	0·018	1610 (1208–2138)	0·22 (0·17–0·30)	48 561 (43 076–55 250)	6·75 (5·98–7·68)
Reduce repeat sexual partnerships by 0·5 times in 25% of MSM	139 700	..	..	..	..	..	..	..	..

(Table 2 continues on next page)

	Number of participants*	Number of infections prevented†	Proportion of infections prevented (%)‡	Total infections	Unit effect§	New infections in 2020	HIV incidence in 2020 (%)	Number with HIV in 2020	HIV prevalence in 2020 (%)
(Continued from previous page)									
Test once a year in 25% of high-activity MSM	74 800	..	..	..	..	..	..	..	..
(3.10) Reduce repeat sexual partnerships, test once a year, and test and treat	217 700	6879 (5213–9062)	40·6 (30·7–53·4)	10 029 (7947–12 604)	0·032	1 060 (823–1 348)	0·15 (0·11–0·19)	45 550 (40 729–51 080)	6·32 (5·66–7·11)
As in scenario 3·9	214 500	..	..	..	..	..	..	..	..
Added: test and treat in 25% of diagnosed MSM	3 200	..	..	..	..	..	..	..	..
(3.11) Reduce repeat sexual partnerships and test and treat, but with (risk compensation) less HIV testing	142 900	3729 (2706–5 104)	22·0 (16·0–30·1)	13 072 (10 272–16 582)	0·026	1732 (1328–2241)	0·24 (0·18–0·31)	48 610 (43 186–54 611)	6·75 (6·00–7·59)
Reduce repeat sexual partnerships by 0·5 times in 25% of MSM	139 700	..	..	..	..	..	..	..	..
Test and treat in 25% of diagnosed MSM	3200	..	..	..	..	..	..	..	..
(Risk compensation) reduce HIV testing frequency by 0·5 times in 25% of high-activity MSM	..	..	..	..	..	..	..	..	..
(3.12) Reduce repeat sexual partnerships and test and treat, but with (risk compensation) less HIV testing and (risk compensation) no condom use with repeat sexual partners	142 900	2681 (1751–3917)	15·8 (10·3–23·1)	14 124 (11 231–17 837)	0·019	1932 (1503–2484)	0·27 (0·21–0·35)	49 625 (44 075–55 910)	6·90 (6·12–7·77)
As in scenario 3.11	142 900	..	..	..	..	..	..	..	..
Added: (risk compensation) completely stop using condom with repeat sexual partners in all ART treated MSM	..	..	..	..	..	..	..	..	..

Data are median (IQR), unless otherwise indicated. Estimates were derived from 1093 simulations. PrEP=pre-exposure prophylaxis. MSM=men who have sex with men. ART=antiretroviral therapy. *The total number of participants covered by each intervention during the intervention period. For the combined interventions, this number is simply the sum of the coverage of the individual interventions. The number of test-and-treat participants represents only those who were treated with ART early in their disease course because of the programme. †Numbers were derived from the difference between the median estimates of infections in the status-quo scenario and the numbers of infections in the scenarios with interventions. ‡Percentages were calculated by dividing the median estimates of infections in the status-quo scenario by the number of infections prevented by the interventions. §Represents the number of infections prevented per programme participant.

***Table 2*: Estimated number of HIV infections prevented in the practical scenarios during 2014–20**

would reduce the probability that non-PrEP susceptibles had serodiscordant relationships, particularly with undiagnosed MSM. Combining the two risk compensations from scenarios 3.6 and 3.7 resulted in the incidence effect of 22·3% (scenario 3.8; table 2).

In scenario 3.9, we assumed that 25% of the entire MSM population reduced repeat sexual partnerships by half, and 25% of high-activity MSM had an annual HIV test. The effect was 22·2% in this scenario (table 2). When the test-and-treat programme with 25% coverage was added to scenario 3.9, the effect increased to 40·6% (scenario 3.10; table 2). However, the benefit of early ART was completely negated if high-activity men tested for HIV half as frequently (scenario 3.11; table 2). If even more risk-compensation behaviour took place, with the assumption that all ART-treated MSM completely stopped using condoms with repeat sexual partners on the basis of the benefit of immediate ART, the effect would fall to 15·8% (scenario 3.12; table 2).

The number of new infections prevented was sensitive to sexual risk compensation, particularly an increase in the number of repeat sexual partners. Most interventions could tolerate up to 75% or more increase in both risk compensations before the benefits were completely negated. However, the sensitivity of the model outcomes to decreasing frequency of HIV testing was relatively less pronounced compared with the sexual risk compensation (appendix, p 19).

Discussion

Our analysis confirmed the importance of implementation of a combination of interventions for effective HIV control in MSM.[13,17] The provision of PrEP as part of a combination strategy, even to a quarter of highly sexually active individuals, could prevent more than 7000 new HIV infections in the UK before the end of this decade. The relatively small coverage the programme requires is feasible because around half of

MSM in the UK have shown interest in participating in PrEP[18] and treatment-as-prevention programmes.[19] Combined programmatic launch would be aided by the fact that the most at-risk men are more likely to use PrEP than are other high-risk MSM.[20]

One of the main concerns about PrEP is that risk compensation could reduce the effectiveness of the intervention.[21] Our risk-compensation analyses suggested that a substantial increase in unprotected anal intercourse would be needed to negate the population-level benefits of PrEP. However, in reality, the negative effect of risk compensation could be multiplied, for example, in PrEP users with poor drug adherence in whom there is an increase in unsafe sex and number of partners simultaneously. Thus, approximation of increased risk-taking in real-world situations, with the behavioural insights gathered from clinical trials, is highly important but might require more appropriate study designs other than a conventional longitudinal analysis.[22] With sufficient knowledge and understanding, the complementary risk-reduction programmes could be tailor-made to help adjust perceptions of risks and benefits underlying the mechanism of risk compensation in PrEP users.

Another issue regarding PrEP is its protective effectiveness against HIV. In the present study we assumed a baseline effectiveness of 44% for the daily tenofovir and emtricitabine, which was suggested by a clinical trial in MSM in six non-European countries.[16] The HIV protective effects of PrEP relied greatly on drug adherence of programme participants,[14,16] which could differ greatly between the trial and actual implementation in the UK. Findings from the PROUD open-label trial suggested a relative incidence reduction of 86% in participants who received PrEP immediately compared with those who received PrEP after a 12 month deferral period.[4] Moreover, the PrEP programme is not a stand-alone intervention, but rather a combination of several components including medicine use, HIV testing, motivational interviewing, and risk reduction. The effectiveness of PrEP will thus rely greatly on the quality of these complementary programmes and might exceed our estimates if all are successfully adopted.

By comparison with PrEP, our findings showed that the test-and-treat programme has a smaller effect on HIV prevention at the population level, which is consistent with modelling studies in other settings.[23,24] This finding might be explained by the already small contribution of MSM with diagnosed HIV to total infections,[3] because after diagnosis there are reductions in high-risk behaviours, and many of these men in whom infection is diagnosed begin ART promptly, especially as the CD4 count threshold for treatment eligibility has changed in the UK.[25] Moreover, now that the individual benefit of immediate ART has been established for people with HIV infection, the high proportion of MSM with HIV infection beginning immediate or very early ART is likely to increase still further.

The key strengths of test and treat lie in various aspects. First, the robustness of the programme in relation to risk-compensation behaviour. This robustness could be explained by the benefits of ART in reducing the probability of HIV transmission between serodiscordant couples,[26] which exceed the adverse effects of plausible risk compensation. Second, the capability of the programme to be effective at low coverage makes it suitable for use in various practical situations in which full coverage is almost impossible to reach. Third, because early ART is only offered to diagnosed MSM, the number of participants needed to reach the targeted incidence reduction is much smaller than that needed by other programmes focusing on a pool of susceptibles and undiagnosed men. Finally, test and treat was the only intervention investigated here that, when implemented along with increased HIV testing frequency and coverage, provided additional benefits over the sum of the two independent effects. This result is because of the completely non-overlapping target groups (undiagnosed *vs* diagnosed MSM) between the two interventions and the increased number of diagnosed individuals to be treated early with ART.

In a modelling study in UK MSM, Phillips and colleagues[27] reported that immediate ART would prevent 32% of new infections during 2006–10 compared with our 100% coverage estimates of 24% during 2014–20. The slight difference in the estimates is probably due to different timescales and the underlying assumptions of the interventions. We assumed that men diagnosed at a CD4 cell count of 350 cells per μL or more, except in those with primary HIV infection, had the same ART initiation rate as those diagnosed at counts of less than 350 cells per μL, whereas in Phillips and colleagues' study,[27] ART was initiated immediately in all MSM diagnosed with HIV after 2000. That study also reported a 25% decline in incidence if HIV test rate has been increasing since 2000 until 2010, when 68% of all MSM were tested each year,[27] whereas in our study testing once a year with 50–75% coverage would lower the incidence by 25–30%. Both our and Phillips and colleagues'[27] studies suggested the same 62% incidence reduction at the maximum coverage if more frequent testing and early ART were implemented simultaneously.

The three ambitious 90-90-90 targets proposed by UNAIDS are intended to reduce HIV incidence by 90% by 2030, compared with that in 2010.[28] The first target called for 90% of people living with HIV in 2020 to be aware of their infection.[28] An estimated 84% of MSM living with HIV in the UK in 2013 were aware of their infection, so the 90% target should be achievable in the near future. The other two targets that expected 90% of diagnosed individuals to be treated with ART, and 90% of those receiving ART to achieve an undetectable viral load,[28] have already been reached in the UK.[1] Despite these achievements, the reduction in incidence by 2030 is unlikely without additional interventions. Our baseline

scenario suggested a constant level of 2000–3000 new infections in UK MSM every year up to 2020, with no sign of a decrease. Through using linear regression on our 2014–20 estimates to extrapolate the future incidence, we concluded that at least 50% of MSM would need to be consistently tested annually or to use PrEP to attain a 90% incidence reduction by 2030. Both testing and PrEP strategies each raised the proportion of MSM living with HIV and aware of their infection to around 95% while maintaining the proportion of MSM living with HIV who were on treatment at around 90%. Thus, achievement of the three 90-90-90 targets might not lead to the 2030 goal[29] and, in the UK MSM setting, achievement of and sustaining a 95-90-90 target by 2020 would be required.

Our study has several limitations. First, our analyses are, by necessity, a simplification of the real world, and might overestimate actual programme effectiveness. For illustrative purpose we show results at 100% coverage, but this is clearly unrealistic. However, the overall conclusions remained similar when the coverage was reduced and we also applied a much smaller level of coverage in the practical scenarios to reflect more conservative outcomes. Second, we did not explicitly include the effects of ART resistance[30] and co-infection with other sexually transmitted diseases[31] on HIV transmission. Unless the prevalence of co-infection and drug-resistant strains changes substantially during the intervention period, their effects on the effect of interventions are not likely to be influential. Third, we did not account for the UK regional difference. Although this limitation might not have a substantial effect on the effect of interventions at the national level, the regional difference might play an important part in some specific areas. Fourth, changes of risk within individuals was also not accounted for. High-risk behaviour may be relatively transient and take place occasionally over time. However, this should have no substantial effect on our findings because we saw no evidence of a major fluctuation in the overall proportions of high-risk MSM in the UK over the past decade. Fifth, even with our practical scenarios the scale of the modelled interventions could be practically too large, and a more targeted programme aimed at groups with highest risks could be more feasible. Finally, our analysis did not include cost-effectiveness, which is also crucial to inform public health decision making. That any highly effective programmes against HIV transmission suggested in this study might not be cost effective in the real UK setting is a possibility. Although a simple cost approximation of implementation of the interventions can be done with the estimated numbers of programme participants provided in the tables, further in-depth economic analyses are needed to inform timely and accurate decision making. Future work should include investigation of the effect of changes in other behavioural factors (eg, partnership duration and mixing preferences) on the effect of interventions.

In conclusion, our analysis suggests that a combination of PrEP, expansion of HIV testing, and test-and-treat programmes implemented in small groups of MSM in the UK could prevent thousands from HIV within a few years of implementation, particularly if risk-compensation behaviour is successfully avoided. Integration of this enhanced version of conventional interventions with novel biomedical technologies is likely to deliver the optimum approach to HIV prevention that could determine the future course of the HIV epidemic in the UK.

Contributors

All authors contributed to the research questions and analysis methods. NP created the mathematical model, did the analysis, and drafted the manuscript with contributions from all authors.

Declaration of interests

We declare no competing interests.

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