Institution: King's College London		
Unit of Assessment: 1		
Title of case study: Reducing the incidence of HIV by improving prevention and treatment		
Period when the underpinning research was undertaken:		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Julie Fox	HIV Consultant, Hon. Reader	2010 - to date
Period when the claimed impact occurred: 2014-2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

HIV-1 (human immunodeficiency virus type 1) attacks the body's immune system and, untreated can lead to AIDS (acquired immunodeficiency syndrome). In 2017, nearly 40 million people globally were living with HIV-1 infection, and rates of new infection are declining too slowly to meet UNAIDS targets for reduction. Since 2014, King's College London research has transformed clinical practice and national and international guidance on pre-exposure prophylaxis (PrEP), HIV testing in novel settings (to access hard to reach groups), and early antiretroviral therapy provision in HIV positive individuals to reduce their infectiousness to others. The demonstration that the virus can be fully suppressed by therapeutics, so that individuals are essentially unable to transmit the virus to a partner, led to the term 'Undetectable Equals Uninfectious' (U=U) and global campaigns to raise awareness and reduce the stigma around HIV. Our research has had a major impact on reducing HIV transmission and improving lives of those infected.

2. Underpinning research

In 2017, approximately 37 million people were living with HIV infection worldwide, with 1.8 million new infections that year. There is no effective vaccine to prevent infection, and no cure for those infected. HIV incidence is slowly declining worldwide but did not reach the Joint United Nations Program on HIV/AIDS (UNAIDS) target of fewer than 500,000 new infections per year by 2020. Steep reductions in incidence are still needed to curb the HIV epidemic, particularly in high risk populations including gay men and women. Until 2012, the two mainstays of preventing HIV transmission were use of condoms and regular HIV testing. Despite these interventions, the estimated HIV incidence among gay and bisexual men in the UK reached a peak of around 2,700 (95% CrI 2,200 to 3,200) in 2012. Therefore there was an unmet need for new interventions that both reduced viral acquisition risk for HIV-uninfected individuals and reduced onward transmission risk from those who are HIV infected; and which can also be targeted effectively at hard to reach groups. King's researchers have collaborated on leading international clinical studies, and led important complementary research, across three of the most promising approaches: (i) Pre-exposure prophylaxis; (ii) HIV testing; (iii) Treatment as prevention.

Demonstrating that 'Pre-exposure prophylaxis' (PrEP) reduces HIV acquisition. Following the first trial to evaluate the potential of drugs taken prophylactically (PrEP) to prevent HIV acquisition, which in 2008 reported 48% efficacy of Truvada (TDF/FTC) in gay men, King's in partnership with UCL and other UK-based institutions to form the PROUD consortium to evaluate Truvada in a real life setting. As part of the consortium, we evaluated the efficacy of daily Truvada PrEP treatment in a randomised control trial (n=544 individuals) or immediate versus deferred PrEP, within which King's was one of the highest recruiting clinical centres. The study showed 88% efficacy for this drug: the highest efficacy found in any daily PrEP study globally to date **(1)**.

Demonstrating that adopting PrEP is cost effective for national health services: Despite the compelling results of the PROUD study and other trials, many governments were reluctant to endorse PrEP because (i) of the cost of Truvada; (ii) of a focus on treating people living with HIV in resource-limited settings and (ii) initial PHE modelling suggested PrEP was not cost effective when considering total lifetime cost versus the cost of HIV treatment across a population (UK). Consequently, at the request of the WHO, King's participated in a formal review of efficacy data

on a cheaper PrEP drug (tenofovir [TDF] monotherapy), which had been studied widely in heterosexual populations but much less so in gay men. King's provided detailed pharmacokinetic analysis (explaining how a drug behaves in the body) on the only 2 cases of TDF PrEP failure globally at the time **(2)**. This study showed that TDF PrEP failure occurred in gay men despite good drug levels, raising concern about its use in gay men. Given concerns about the initial modelling on cost-effectiveness of PrEP at population level, King's also led a re-evaluation of the cost of HIV infection to national health services. The data is now available to update the 15-year-old HIV lifetime cost data upon which the original cost effective modelling was based; and to populate more accurate PrEP cost effectiveness models **(3)**.

Analysing the potential of opt-out HIV testing to reduce the undiagnosed fraction of HIV infections and access hard to reach groups. An important part of reducing onward transmission risk from those who are HIV infected is to test and diagnose as many individuals as possible (particularly those from high risk populations). This has been limited by accessing hard to reach groups, who are affected by stigma and people being unaware of their high risk. In 2011, King's led a study analysing the impact of missed opportunities for HIV diagnosis at Guys & St Thomas' NHS Trust (GSTT), reviewing all HIV related hospital admissions in a 12 month period: the results showed there were multiple missed opportunities for early HIV diagnosis, resulting in high financial cost to the Trust and high morbidity to the individuals **(4)**. 41% of new HIV hospital inpatient diagnoses had presented to local healthcare services at least once within the previous 12 months and not been tested for HIV, and 37% of these had an HIV indicator condition (for example lymphoma or forms of pneumonia [PCP]). We found that the mean cost of admission for those diagnosed as an inpatient was £36,625 (range £331-223,000). The total cost for the 12 inpatients, who had presented to services in the preceding year but had not been tested was £439,500.

The concerning number of missed opportunities to test for HIV within London's high-prevalence HIV population was concerning, and King's and GSTT subsequently led urgent engagement of primary, secondary and tertiary healthcare systems (across London and at national UK HIV meetings) to increase hospital-based HIV testing and prevent late-stage diagnoses. The results reached national news and prompted NHS Trusts across the UK to encourage staff to report missed opportunities for HIV tests as clinical incidents (the official system for taking action on clinical issues): this meant that Trusts were, for the first time, collecting data on missed opportunities for HIV testing around the UK. In 2011, King's collaborated with 6 A&E departments across the UK to evaluate opt-out HIV testing. We found 1.4% HIV and 2.4% HCV (hepatitis C) prevalence in people attending A&E departments **(5)**. These high levels of infection in a general A&E population provided data to support cost effectiveness of opt-out testing, since adopted by A&E centres in areas of high HIV prevalence across the UK (see section 4).

Demonstrating that 'Treatment as prevention' (TASP) in HIV infected people dramatically reduces onward transmission. Treating those who are HIV infected could have an additional protective effect for sexual partners, if the treatment also reduced onward transmission risk. King's collaborated with UCL and other UK and EU institutions to run the largest prospective trial to establish whether HIV treatment prevents transmission, and ran one of the clinical sites. The PARTNER trial prospectively followed up HIV serodiscordant gay male couples where the HIV positive partner was receiving anti-retroviral treatment (ART), to see whether HIV was transmitted to their uninfected partner. The results showed zero transmissions after enrolling almost 800 gay couples who had sex more than 77,000 times without condoms **(6)**. This headline result has been termed 'undetectable equals uninfectious' and adopted globally by WHO and all HIV stakeholders.

Demonstrating that concurrent STIs do not compromise the protective effect of TASP. King's (in parallel) led a study to evaluate whether this protective effect of ART is compromised by concurrent bacterial sexually transmitted infections (STIs) in HIV positive men. The study included 42 individuals and carried out rectal HIV viral load swabs on HIV positive gay men with and without rectal bacterial STI. King's showed conclusively that concurrent bacterial STIs do not increase HIV infectiousness in an HIV positive person who is receiving ARV ($p=0.4$) **(7)** This was an important result because the rates of bacterial STIs are very high among HIV positive men who have sex with men (MSM) - for example in 2009 over three quarters of MSM diagnosed with LGV (caused by Chlamydia species) were co-infected with HIV. Thus this result was crucial for assuring the results of the PARTNER trial for implementation in a real-world context. Taken together, this

research has been highly influential, leading to widespread public health campaigns and helping to reduce stigma towards people with HIV.

3. References to the research

1. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, Sullivan AK, Clarke A, Reeves I, Schembri G, Mackie N, Bowman C, Lacey CJ, Apea V, Brady M, **Fox J** et al. (2015). Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 2016 Jan 2;387(10013):53-60.
2. **Fox J**, Brady M, Alexander H et al. (2016). Tenofovir Disoproxil Fumarate Fails to Prevent HIV Acquisition or the Establishment of a Viral Reservoir: Two Case Reports. Infect Dis Ther 5(1):65-71.
3. **Fox J,** Tiraboschi JM, Herrera C et al. (2016). Pharmacokinetic/Pharmacodynamic Investigation of Single-Dose Oral Maraviroc in the Context of HIV-1 Pre-exposure Prophylaxis. J Acquir Immune Defic Syndr. 73(3):252-257.
4. **Read PJ, Armstrong-Jones D, Tong CY, Fox J.** (2011). Missed opportunities for HIV testing - a costly oversight. QJM 104(5):421-4
5. **Naylor E, Axten D, Makia F, Tong W, White J, Fox J**. (2011). Fourth generation point of care testing for HIV: validation in an HIV-positive population. Sex Transm Infect; 87(4):311
6. Rodger AJ, Cambiano V, Bruun T et al. PARTNER Study Group. (2016). Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. JAMA12;316(2):171-81. Erratum in: JAMA. 2016 Aug 9;316(6):667. Erratum in: JAMA 2016 Nov 15;316(19):2048.
7. **Davies O, Costelloe S, Cross G, Dew T, O'Shea S, White** J, **Fox J**. (2017). Impact of rectal gonorrhoea and chlamydia on HIV viral load in the rectum: potential significance for onward transmission. Int J STD AIDS 28(10):1034-1037.

4. Details of the impact

Fewer people have acquired HIV as a result of introducing these new approaches to reduce transmission. There has been a striking overall reduction in new HIV cases in the UK **[A1]**, with Public Health England (PHE) reporting in 2017 that new diagnoses decreased from 5,280 new cases in 2016 to 4,363 **[A2]**. Between October 2015 and September 2016, HIV diagnoses fell by 32% compared with the previous year, among MSM attending selected London sexual health clinics (from 880 to 595; $p = 0.014$ for test of linear trend in diagnoses by quarter) **[A1, A3]**. This decline has been attributed to a combination of introducing treatment as prevention (TASP) for HIV positive individuals, increased HIV testing and a rapid increase in PrEP uptake: King's has made an important contribution to impactful research in all three areas, collaborating on two of the most globally important large-scale clinical trials and leading clinical studies on complementary questions relevant to implementation of these approaches.

Changing national and international guidelines to give more people access to PrEP in the UK and internationally. The PROUD study **(1)** is widely viewed as the most important real-life PrEP study globally; the clear results were a key piece of evidence leading to changes in official guidelines on reducing HIV transmission. In the UK, the British HIV Association (BHIVA) – responsible for national clinical guidance on HIV – produced a statement in 2016 endorsing the use of PrEP and subsequently developed NICE-approved guidelines published in 2018, which are now followed by all clinicians working in the UK **[B1]**. The European AIDS Clinical Society (EACS) 2018 treatment guidelines include updated guidance on PrEP **[B2]**. The World Health Organisation (WHO) early release (2015) and subsequent consolidated guidelines (2016) included recommendation for use of PrEP in a wider population, citing PROUD results amongst the body of evidence reviewed to formulate these recommendations **[B3]**.

Contributing evidence that led to the UK Government PrEP implementation trial and investment in provision of PrEP through the NHS. So compelling were the results of the PROUD study **(1)** that, in 2016, the UK Government allocated £10 million to the large-scale PrEP Implementation Trial (citing PROUD), which ran from 2016-2019 and opened availability of PrEP through the NHS to 10,000 gay men **[C1]**. In January 2019, the Government announced their commitment to achieving zero HIV transmission by 2030 – setting out that reaching this goal would depend on continuing prevention efforts including making PrEP available to everyone who needs

it **[C2]**. In March 2020 following the reporting of the PrEP Implementation Trial, the Government announced provision of a further £16 million to make PrEP available on the NHS **[C3]**.

Influencing licensing decisions and recommendations on specific ARV drugs for PrEP. King's research has influenced decisions on whether or not specific anti-retroviral (ARV) drugs were made available. The PROUD study was included in the 2016 NICE Evidence Review of Truvada **[D1]**, and part of the evidence submitted leading to Truvada being licensed by the EMA in 2016 for use as PrEP **[D2].** King's research on Maraviroc **(3)** – another class of HIV prevention drug – demonstrated that this drug was not as effective as on demand PrEP. This prevented Maraviroc being investigated in a costly large phase 4 trial and prevented its recommendation for PrEP usage by regulators or national health services **[D3]**.

Informing development of guidelines for use of PrEP drugs for Post-Exposure Prophylaxis (PEP). King's research on HIV prevention **(2,3)** led to Dr Fox's involvement in developing clinical guidance for the newer use of PrEP drugs for Post Exposure Prophylaxis (PEP), which involves treating someone recently exposed to HIV with a combination of ARV drugs that may prevent an infection developing. King's co-authored the first clinical UK BHIVA PEP guidelines (2015, 2019) **[E1,2]** and led a PEP review for the BMJ (2017) **[E3]**. The BHIVA guidelines are now used by all sexual health institutions across the UK and recommended by the British Association for Sexual Health & HIV to healthcare professionals **[E2]**.

Changing clinical practice to ensure that more people are getting tested for HIV, with focus on hard to reach populations. The estimated number of people with undiagnosed HIV infection in the UK reduced from 13,300 (CrI 10,600 to 18,200) in 2015 to 10,400 (CrI 8,400 to 15,700) in 2016, with most of the decline in London apparent in gay and bisexual men, and black African heterosexual women **[F1]**. King's work contributed to the following efforts with continuing impact:

National reporting of missed diagnoses introduced: Following presentation of King's findings on missed opportunities for diagnosing HIV in hospitals **(4)** at the 2010 British HIV conference, reporting in the Guardian newspaper raised the public profile of this issue. BHIVA subsequently carried out a national audit and produced guidance on recording later HIV diagnoses. Collectively this triggered NHS Trusts to start ensuring missed HIV diagnoses were formally reported as serious untoward incidents (SUIs) – serious clinical events that put lives at risk: these go to Trust leadership and must be acted on within 24 hours, meaning that root cause analysis is now carried out on each case **[F2]**. As well as introducing systematic data collection, this has reduced stigma by normalising HIV testing and helped increase testing in all healthcare settings as evidenced by the large number of hospitals adopting opt out HIV testing in A&E departments **[F3]**.

Going Viral campaign: In 2017 King's collaborated on the Going Viral campaign across 9 NHS Trusts across the UK to encourage opt-out HIV testing in A&E: Uptake of opt out testing services in A&E was >90% in these 9 NHS Trusts (GSTT, Royal London, Whipps Cross, Newham General, Homerton, King George, Queens Hospital, St James' University Hospital and Gartnaval University Hospital **[G]**. King's-GSTT was the first centre in the UK to adopt this approach as routine care. Local site information for GSTT shows that this represents a 95% increase in HIV tests carried out by A&E in a 12-month period **[G]**.

Opt-out testing in A&E adopted by NHS Trusts around the UK: King's research on the high levels of HIV infection in a general A&E population also provided data to support cost effectiveness of opt-out testing **[4,5]**. Guys and St Thomas' NHS Trust was the first Trust in the UK to introduce opt-out HIV testing in A&E; this has since been introduced by Trusts throughout the UK in high HIV prevalence areas **[F3]**. As a result of the research on this subject, opt-out HIV testing in A&E is now recommended in high risk populations (all areas where the local rate of HIV infection is above a certain threshold) in the national BHIVA guidelines and thus been implemented UK wide **[H1].** King's A&E testing research **[4,5]** also led National British Association for Sexual Health (BASH) and the Royal Society of Emergency Medicine in 2020 to recommend that HIV testing be offered to millions of people living in areas of the UK with a high prevalence of HIV **[H2, H3]**.

Supporting increased community testing: Community point of care (POCT) HIV testing has also increased, and King's has supported this implementation process locally, evaluating POCT tests for their ability to detect early infection, providing guidance on which tests to use, and what to say or explain when using them in the community. For example, King's worked with community

healthcare providers to determine the social factors influencing uptake of HIV testing – whether people were willing to be tested, how they would feel most comfortable accessing tests; a recent survey in BAME London communities revealed interest in vending machine tests, particularly in specific places within the community such as hairdressers or barbers **[I]**.

Service provision guidance on HIV testing: As a result of the work in this area, reviews of late HIV diagnosis were included in the 2018 BHIVA Standards of Care for People Living with HIV (which provides guidance of running HIV services) **[J1]** and in 2019, a King's-led UK-wide audit of late HIV diagnoses was carried out by BHIVA **[J2]**.

Providing expert advice to policy discussions and development. On the basis of her leadership in this area – combining expertise of lab-based drug trials with real-world implementation – King's researcher Dr Fox has been asked to contribute to a number of policy and clinical discussions, including national committees for UK PEP and PrEP guidelines. Dr Fox is an advisor on WHO technical groups for HIV testing, PrEP (implementation, monitoring), HIV vaccine development and STI treatment; and on WHO guidelines for HIV testing in the presence of PrEP, the role of tenofovir monotherapy in PrEP and STI management in the era of PrEP **[K]**.

Stigma surrounding HIV has reduced as a result of the term undetectable = uninfectious. King's research on TASP, particularly collaboration on the PARTNER study showing that undetectable means uninfectious to transmit, has been especially influential in tackling stigma around HIV. This finding changed UK, EU and WHO HIV treatment guidelines so that TASP was an indication for starting ART, meaning HIV treatment is now offered to everyone irrespective of CD4 count, with accompanying mass public health campaigns **[L]**. The work also led to the coining of the U=U slogan (from undetectable= uninfectious), and the associated global campaign to raise public awareness; these efforts are reducing HIV stigma across all populations by reducing anxiety about transmission from HIV positive people, and the phrase U=U is now used globally by stakeholders to promote HIV awareness **[L]**. King's researchers have been directly involved in shaping evidence-based public facing communication and advocacy to those living with HIV, advising the HIV treatment information base (i-base.info) and engaging research patient groups and HIV community organisations **[L]**.

5. Sources to corroborate the impact

[A] Evidence on the decline in rates of HIV transmission in the UK: A1. Brown AE, et al. Euro Surveill. 2017;22(25):30553 [PDF]; A2. PHE report on HIV in the UK (2017) [PDF]; A3. Nwokolo N et al. (2018). Rapidly declining HIV infection in MSM in central London [PDF]
[B] Recommendation of PrEP in national and international guidelines: B1. British HIV Association (BHIVA) PrEP statement (2016) and guideline (2018) [PDF]; B2. (EU) EACS 2018 HIV treatment guidelines; B3. WHO PrEP guidelines (2015, 2016) and policy briefing [PDF].
[C] UK Government investment in PrEP implementation and provision through the NHS: C1. UK PrEP implementation trial, 2016-19; C2. UK Government commit to zero HIV transmissions by 2030 (2019); C3. UK Govt. commits £16million funding for PrEP (2020) [PDF].
[D] Influencing recommendations on specific PrEP drugs: D1. NICE evidence review of Truvada (2016). D2. Example of regulatory approval for PrEP drugs; D3. Guidance on PrEP drugs. [PDF]
[E] Developing PEP guidelines: E1. BHIVA guidelines 2015, 2019. E2. BMJ review (2017) [PDF]
[F] Changing clinical practice to increase HIV testing: F1. PHE data on undiagnosed HIV infections (2016); F2. Example of SUI reporting; F3. Example of Trusts adopting opt-out testing. [PDF]
[G] The "Going Viral" Campaign: Orkin C, et al. HIV Med. 2016 Mar;17(3):222-30; Awards recognising effectiveness of the campaign [PDF.]
[H] National and international HIV testing guidelines: H1. BHIVA HIV Testing guidelines (2020) [PDF]; H2. BASH HIV Testing guidelines (2020) [PDF]; H3. RSEM recommendation (2020) [PDF].
[I] Supporting community testing: Lee MJ, et al. Int J STD AIDS. 2020 31(2):158-165. [PDF]
[J] Informing service provision for HIV services: J1. BHIVA Standards of Care for People Living with HIV 2018. J2. BHIVA UK wide audit of late HIV diagnoses, Ming et al. 2019 [PDF]
[K] WHO Meeting report (2016) corroborating King's researcher as an expert advisors [PDF]
[L] Tackling stigma and raising public awareness: L1. U=U campaign information; L2. Lancet editorial on U=U campaign. L3. Example of U=U endorsement, CDC (US). [PDF]