Institution: University College London		
Unit of Assessment: 2 - Public Health, Health Services and Primary Care		
Title of case study: Advancing international HIV treatment and prevention and reducing new UK infections among men who have sex with men.		
Period when the underpinning research was undertaken: Between 2009 and 2016		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s):**	**Period(s) employed by submitting HEI:**
Sheena McCormack	Professor of Clinical Epidemiology	Between 2013 and present
David Dunn	Professor of Medical Statistics	Between 2013 and present
Abdel Babiker	Professor of Epidemiology & Medical Statistics	Between 2013 and present
Alejandro Arenas-Pinto	Principal Research Fellow	Between 2008 and present
Professor Sarah Pett	Clinical Senior Lecturer	Between 2013 and present
Valentina Cambiano	Associate Professor	Between 2008 and present
Andrew Phillips	Professor of Epidemiology and Biostatistics	Between 1991 and present
Dr Richard Gilson	Professor of Sexual Health and HIV Medicine	Between 2014 and present
Professor Anne Johnson	Chair and Vice- Dean, External Relations	Between 2002 and present
Period when the claimed impact occurred: Between 2015 and December 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

UCL's PROUD trial, led by researchers from the MRC Clinical Trials Unit at UCL and Public Health England (PHE), has demonstrated the effectiveness of pre-exposure prophylaxis (PrEP) in reducing the incidence of HIV among men who have sex with men (MSM). The START trial – co-led by UCL researchers – demonstrated that starting antiretroviral therapy (ART) in HIV-positive people who still have preserved immune systems can halve their risk of later developing serious disease. These studies have driven changes in national and international treatment guidelines, with WHO data showing that the proportion of low and middle income countries applying a 'treat all' policy as a result of these findings has doubled from 33% to 84%. Meanwhile in the UK, the combined impact of ART for prevention and PrEP have resulted in a 71% reduction in HIV incidence among MSM.

2. Underpinning research

In the 2000s, the number of men who have sex with men (MSM) diagnosed with HIV in the UK was increasing, and by 2015 had reached almost 3,500 per year. From 2009, two strategies using antiretroviral drugs to reduce HIV incidence - namely 'test and treat' and pre-exposure prophylaxis (PrEP) - were being considered in addition to the long-term prevention policy of promoting condom use. However, there were several uncertainties.

A key element of approaches to preventing HIV infection is 'treatment as prevention': to promote antiretroviral therapy (ART) to everyone newly diagnosed with HIV in order to minimise the risk of them transmitting the virus to others. To get maximum benefit from this strategy it is necessary to scale up HIV testing in parallel. In 2009, it was not clear that people with HIV who had a relatively preserved immune system (CD4 lymphocyte count > 350 cells /mm^3) would gain clinical benefit from starting ART, and thus the policy was to start ART only when the CD4 count had declined to below this level. It was also unclear whether treatment as prevention would be effective, due to

the fact that it was understood that a high proportion of new infections came from recently infected people who were yet to be diagnosed or treated.

PrEP was shown in a placebo-controlled trial published in 2010 to have partial efficacy in preventing HIV in MSM couples. However, there was concern that this trial could have over-estimated the real-life effect because PrEP users might increase the number of partners with whom they did not use a condom. Conversely it was also unknown if the trial had under-estimated the real-life effect of PrEP, if in fact users tended to be more adherent when they knew they were taking an active drug rather than being involved in a placebo-controlled trial. To address these uncertainties, UCL academics co-led several key studies, analyses and modelling work. In particular, they led and co-led two major studies, as follows:

(i) The international **Strategic Timing of Antiretroviral Therapy (START) trial**, which involved 4,685 HIV positive people from 35 countries, all of whom had a CD4 count above 500/mm^3. Half of participants were randomised to start ART straight away, while the other half were randomised to wait until their CD4 count had dropped below 350/mm^3 before beginning ART. Findings demonstrated that among those who started ART immediately, only 42 patients (1.8%) died or developed serious disease (either AIDS-related or non-AIDS related) compared with 96 (4.1%) patients in the deferred-initiation group. This proved that people with CD4 count > 500 /mm^3 will have an individual clinical benefit from starting ART **[R1]**.

(ii) The **Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD) trial** - an open-label, randomised trial involving 544 HIV-negative MSM participants in England. Half the participants (275) were randomly assigned to receive daily combined PrEP (tenofovir disoproxil fumarate and emtricitabine) immediately while the other half (269) deferred receiving PrEP for one year. Three HIV infections occurred in the immediate group compared with 20 in the deferred group (an 86% relative reduction). The team also detected no difference in the occurrence of sexually transmitted infections between the groups, despite a suggestion of risk compensation among some PrEP recipients. PROUD therefore demonstrated that PrEP is 86% effective in MSM in the UK in a real-life context **[R2]**.

Alongside this, UCL led modelling studies in collaboration with Public Health England (PHE) **[R3]**, **[R4]**. The findings from this research predicted that if HIV testing and diagnosis rates were substantially increased and ART started immediately after diagnosis, incidence of HIV would decline substantially despite the fact that the majority of infections did indeed come from undiagnosed men. Further modelling studies carried out by the UCL team showed that such a policy was cost effective **[R4]**. Using a simulation model calibrated with UK data on HIV in MSM, the UCL team projected outcomes according to future alternative HIV testing and ART initiation scenarios to 2030. They concluded that to reduce incidence to one per 1000 person-years by 2030, the percentage of HIV-positive MSM with viral suppression must increase from below 60% to 90%, assuming no rise in condomless sex. The modelling showed that substantially increasing HIV testing and initiating ART at diagnosis would achieve this **[R4]**. This was extended to show that use of PrEP in MSM was also cost effective **[R5]**. The UCL analysis showed that introduction of PrEP programme with sexual event-based use of PrEP for HIV-negative MSM at high risk of infection, would result in a GBP1bn cost saving, avert 25% of HIV infections and lead to a gain of 40,000 discounted QALYs over an 80-year time horizon **[R5]**.

3. References to the research

[R1] The INSIGHT START Study Group (Lundgren J.D., Babiker A.G., Gordin F., Emery S., Grund B., Sharma S., Avihingsanon A., Cooper D., Fätkenheuer G., Llibre J.M., Molina J.M., Munderi P., Schechter M., Wood R., Klingman K.L., Collins S., Lane H.C., Phillips A.N., Neaton J.D.) (2015). 'Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection'. *New England Journal of Medicine*. **373**, 795-807. DOI: http://doi.org/10.1056/nejmoa1506816 Google Scholar citations: 1959

[R2] McCormack, S., Dunn, D.T., Desai, M., Dolling, D.I., Gafos, M., Gilson, R., Sullivan, A.K., Clarke, A., Reeves, I., Schembri, G., Mackie, N., Bowman, C., Lacey, C.J., Apea, V., Brady, M.,

Fox, J., Taylor, S., Antonucci, S., Khoo, S.H., Rooney, J., Nardone, A., Fisher, M., McOwan, A., Phillips, A.N., Johnson, A.M., Gazzard, B., Gill, O.N. (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*. **387** (10013), 53-60. DOI: http://doi.org/10.1016/S0140-6736(15)00056-2 Google Scholar citations: 1181

[R3] Phillips, A.N., Cambiano, V., Nakagawa, F., Brown, A.E., Lampe, F., et al. (2013). 'Increased HIV Incidence in Men Who Have Sex with Men Despite High Levels of ART-Induced Viral Suppression: Analysis of an Extensively Documented Epidemic'. *PLoS ONE*. **8**(2), e55312. DOI: http://doi.org/10.1371/journal.pone.0055312

[R4] Phillips, A.N., Cambiano, V., et al (2015). 'Potential impact on HIV incidence of higher HIV testing rates and earlier antiretroviral therapy initiation in MSM'. *AIDS* **9**(14), 1855–1862. DOI: http://doi.org/10.1097/QAD.0000000000000767

[R5] Cambiano, V., Miners A., Dunn D., McCormack S., Ong K.J., Gill O.N., Nardone A., Desai M., Field N., Hart G., Delpech V., Cairns G., Rodger A., Phillips A.N. (2018). 'Cost-effectiveness of pre-exposure prophylaxis for HIV prevention in men who have sex with men in the UK: a modelling study and health economic evaluation'. *Lancet Infectious Diseases*. **18**(1), 85-94. DOI: http://doi.org/10.1016/S1473-3099(17)30540-6

4. Details of the impact

Evidence from the UCL-led PROUD and START studies (the latter co-led with four other universities) have led to changes in clinical guidelines in the UK and internationally, preventing thousands of new infections and transforming the futures of millions more people living with HIV.

UK clinical guideline changes as a direct result of the UCL work

The British HIV Association (BHIVA) updated its treatment guidelines in 2015 (co-authored by UCL's Professor Andrew Phillips), to recommend that people diagnosed with HIV should 'begin ART immediately, regardless of CD4 count' in both chronic HIV and in primary treatment of HIV **[S1]**, underpinned by the START findings **[R1]**. BHIVA published the PrEP guidelines in 2018, together with the British Association of Sexual Health and HIV **[S2]**. UCL's Dr Valentina Cambiano and Professor Sheena McCormack were among the co-authors of the guideline and PROUD findings are embedded throughout the recommendations as key evidence. This includes citation of **[R2]** as underpinning evidence to recommend that PrEP should be offered to MSM and trans women at high risk of HIV infection, on PrEP dosing schedules and lead-in times, and contributed to the guidance on adherence to PrEP including support and education, and the settings and context for administering PrEP **[S2]**.

Following the change in treatment guidelines, based on the START trial, the proportion of MSM with HIV who have undetectable viral load (meaning their infection is fully controlled and they are not sexually infectious) was estimated by Public Health England (PHE) to have increased from 48% in 2011 to 87% in 2017 in their report 'Progress towards ending the HIV epidemic in the UK' **[S3]**. Changes to clinical practice as a result of the START and PROUD findings feature prominently in this report, which states: *"The progressive implementation of combination HIV prevention is the principal explanation for the fall in HIV incidence in gay and bisexual men since 2012… Current key components of combination HIV prevention in the UK include: condom provision, pre-exposure prophylaxis (PrEP), expanded HIV testing and prompt initiation of antiretroviral therapy (ART) after diagnosis."* **[S3]**.

UK roll-out of PrEP: Early use of PrEP was almost entirely confined to those individuals enrolled in the UCL-led PROUD trial itself. From 2017, PrEP has been available for free through the PrEP Impact Study, which includes UCL's Dr Richard Gilson and Professor Sheena McCormack among its co-investigators, and which has informed planning of the PrEP programme in England. In March 2020, the Department of Health and Social Care announced that PrEP would be provided by the NHS: *"Local authorities will receive GBP16m in 2020 to 2021 to deliver the preventative HIV treatment PrEP. The funding from the Department of Health and Social Care will ensure anyone*

who is at a high risk of contracting HIV will receive PrEP from their local sexual health clinic to reduce their risk of getting the virus." In October 2020, the English Department of Health made available a PrEP grant to support local authorities in England to deliver routine commissioning of PrEP in 2020 to 2021. PrEP has been available as part of a trial since 2017 and on NHS prescription (generic versions of the drug) in Wales since 2018 according to Public Health Wales; as part of a pilot trial in Northern Ireland since 2018 overseen by Health and Social Care in Northern Ireland; and has been prescribed to anyone at high risk of HIV infection by the NHS in Scotland since 2017 **[S4]**. In December 2020, the AIDS Vaccine Advocacy Coalition (AVAC)'s PrEP Watch Initiative estimated that between 17,500 and 18,500 people are now receiving PrEP in the UK **[S4]**.

Dramatic reduction of new diagnoses in MSM observed in the UK: The UCL-led team estimated, through modelling, that the number of incident cases of HIV in MSM in England and Wales was approximately 3,500 in 2015, although PHE had slightly lower estimates of 2,500 from a separate modelling exercise. Using the more conservative figure from the latter approach, the combined impact of ART for prevention and PrEP have resulted in an 71% reduction in HIV incidence among MSM to 800 cases, as stated in PHE's 2019 report 'HIV in the United Kingdom: Towards Zero HIV transmissions by 2030': "*Evidence from a series of randomised-controlled trials, including the jointly PHE-sponsored and partially PHE-funded PROUD Trial, showed that when PrEP is taken consistently, it is highly effective at protecting people who are at a high risk of acquiring HIV."* **[S5]**.

Various clinic-based studies have documented declines of up to 80% in new HIV diagnoses since 2015, including a 2017 study published in *Eurosurveillance* of HIV diagnoses in MSM following adoption of the new guidelines. This reported a 32% annual fall in diagnoses in selected London clinics in 2015 to 2016 compared with 2014 to 2015. This fall coincided with higher HIV testing and rapid initiation of treatment. The authors conclude: *"Intensified testing of high-risk populations, combined with immediately received anti-retroviral therapy and a pre-exposure prophylaxis (PrEP) programme, may make elimination of HIV achievable."* **[S6]**.

No studies have suggested that condom use has increased during this period, or that any other prevention mechanisms might have operated. While the relative impact of ART for prevention and PrEP is uncertain, it is clear that PROUD and START have contributed substantially to changes in policy and practice that have resulted in more than a 50% reduction in the number of new infections in MSM in the UK **[S3]**, **[S5]**, **[S6]**, **[S7]**.

International guideline changes and global uptake of PrEP

START and PROUD have also influenced World Health Organization's 'Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV' (2015), which states: *"The PROUD study, conducted in the United Kingdom and designed to mimic real-life settings, demonstrated that PrEP is feasible and effective and is not associated with significant changes in behavioural risk."* **[S8]**. The studies also influenced a 2017 update to the United States Centers for Disease Control (CDC) guideline on PrEP for the prevention of HIV infection, which cites PROUD as a key piece of evidence for the safety and efficacy of antiretroviral prophylaxis **[S9]**. Both studies led to changes in guidelines, respectively to initiate ART immediately in all people with HIV diagnosed and to recommend PrEP use in HIV negative MSM to prevent HIV.

PrEP first became available through self-purchase online from global pharmacies, and clinics began to actively promote and support use from September 2015, working closely with community organisations. Data collected by the World Health Organization, published in July 2019, for 194 WHO Member States – including 137 low- and middle-income countries (LMICs) – estimated that, by the end of 2020, 95% of all LMICs would have adopted the policy of treating everyone diagnosed with HIV, 115 (84%) LMICs had already put the 'treat all' policy fully into practice and five (4%) LMICs would have implemented this policy in the majority of treatment sites **[S10]**. The 'treat all' policy has been adopted globally and affects 99% of people living with HIV. According to UNAIDS, *"In 2019, 25.4 million* [24.5 million–25.6 million] *people were accessing antiretroviral*

therapy, up from 6.4 million [5.9 million–6.4 million] *in 2009."* **[S11]**. The guideline change as a result of the START trial made a significant contribution to this increase.

Summary: Through two ground-breaking randomised studies, UCL researchers have proven that PrEP is highly effective in reducing the incidence of HIV among MSM, and that starting ART in HIV-positive people at an earlier stage (when their immune systems are relatively preserved) can halve their later risk of dying or developing serious disease. These two findings have had a direct and powerful influence on clinical guidelines across the world and have changed the futures of millions of people who would otherwise have become infected with HIV, lived shorter lives or developed serious diseases.

5. Sources to corroborate the impact

[S1] https://www.bhiva.org/file/jvPQXcViUbtgr/2015-treatment-guidelines.pdf
[S2] https://www.bhiva.org/file/5b729cd592060/2018-PrEP-Guidelines.pdf
[S3] Nash S., Desai S., Croxford S., Guerra L., Lowndes C., Connor N., Gill O.N. 'Progress towards ending the HIV epidemic in the United Kingdom: 2018 report'. November 2018, PHE. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/821273/Progress_towards_ending_the_HIV_epidemic_in_the_UK.pdf.
[S4] PrEP availability in the UK. England: https://www.gov.uk/government/publications/hiv-pre-exposure-prophylaxis-prep-grant-determination-2020-to-2021; Scotland: https://prep.scot/; Wales: https://www.friskywales.org/wales-prep-project.html; Northern Ireland: https://www.iwantprepnow.co.uk/prep-on-the-nhs/#ni; PrEP watch UK summary: https://www.prepwatch.org/country/united-kingdom/; PrEP impact study: https://www.prepimpacttrial.org.uk/
[S5] O'Halloran C., Sun S., Nash S., Brown A., Croxford S., Connor N., Sullivan A.K., Delpech V., Gill O.N. 'HIV in the United Kingdom: Towards Zero 2030. 2019 report'. December 2019, Public Health England.
[S6] Brown A.E., Mohammed H., Ogaz D., Kirwan P.D., Yung M., Nash S.G., Furegato M., Hughes G., Connor N., Delpech V.C., Gill O.N. (2017). 'Fall in new HIV diagnoses among men who have sex with men (MSM) at selected London sexual health clinics since early 2015: testing or treatment or pre-exposure prophylaxis (PrEP)?'. *Euro Surveill.* **22**(25), pii=30553. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2017.22.25.30553;
Nwokolo, N., Hill, A., McOwan, A., Pozniak, A. (2017). 'Rapidly declining HIV infection in MSM in central London'. *Lancet HIV*, **4** (11), e482-e483. DOI: http://doi.org/10.1016/S2352-3018(17)30181-9
[S7] Hanum, N., Cambiano, V., Sewell, J., Lampe, F.C., Rodger, A.J., Speakman, A., Nwokolo, N., Asboe, D., Gilson, R., Clarke, A., et al. (2019). 'Substantial decline in HIV incidence between 2015 and 2018 among a prospective cohort of men who have sex with men in England'. *HIV Medicine.* **20**, 58-58 (5: Special Issue Meeting Abstract: p106, April 2019). https://www.bhiva.org/file/5ca73250ec605/P106.pdf
[S8] World Health Organization 'Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV' (2015) https://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en (START featured on page 27)
[S9] US Centers for Disease Control guideline, 2017 update: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf
[S10] https://apps.who.int/iris/bitstream/handle/10665/326035/WHO-CDS-HIV-19.20-eng.pdf?ua=1
[S11] https://www.unaids.org/en/resources/fact-sheet