Institution: University College London		
Unit of Assessment: 2 - Public Health, Health Services and Primary Care		
Title of case study: Transforming global HIV prevention strategies and the lives of millions of people living with HIV.		
Period when the underpinning research was undertaken: Between 2009 and 2019		
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:**
Alison Rodger	Professor of Infectious Diseases/HIV	Between 2009 and present
Andrew Phillips	Professor of Biostatistics	Between 1991 and present
Valentina Cambiano	Lecturer in Modelling and Biostatistics	Between 2008 and present
Period when the claimed impact occurred: Between 2014 and 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Led by research teams in the UCL Institute for Global Health, the PARTNER study signalled a potential end to the HIV endemic by showing conclusively that people whose HIV infection is fully suppressed by antiretroviral drugs have no possibility of infecting sexual partners even when condoms are not used. PARTNER's results now underpin the global U=U (Undetectable=Untransmittable) campaign, WHO and UNAIDS guidelines, and the current US national HIV/AIDS strategy. The UCL team's findings also have a profound impact on the lives of people living with HIV by reducing HIV-related stigma and discrimination; encouraging early testing and treatment; and combatting HIV criminalisation laws which imprison people with HIV, based on outdated assumptions that have been disproved by Rodger and Phillips' work.

2. Underpinning research

The underpinning research was led by UCL Professors Alison Rodger and Andrew Phillips, whose research has showed beyond reasonable doubt that HIV transmission between sexual partners cannot occur, even when condoms are not used, when an HIV positive individual (a person living with HIV; PLWH) is on antiretroviral treatment (ART) with a suppressed viral load. This is all the more remarkable since science cannot prove a negative. However, the strength and quality of evidence from the UCL studies is such as that it is now globally accepted that PLWH on suppressive treatment are sexually non-infectious.

Research gaps addressed by UCL research

As global HIV infections continued to grow between the 1980s and 2000s, from 2009 a strategy called 'Treatment for Prevention', using ART in all PLWH to minimise transmission of the infection to their sexual partners, was being considered. However, there were key uncertainties preventing this policy being implemented, which the UCL team described in full in their 2013 publication **[R1]**. Cohort studies and one randomised clinical trial suggested that HIV-positive heterosexuals on ART with undetectable virus levels were unlikely to transmit HIV, but there were no precise estimates of risk and no data at all for gay men for higher-risk anal sex, as opposed to vaginal sex. A further uncertainty was the preventive role of ART in the absence of condoms, which also effectively prevent HIV transmission. Cost effectiveness was also unknown as guidelines only recommended starting ART at low CD4 counts, but not in all PLWH. Rodger and Phillips conducted the studies outlined below to address these uncertainties.

The PARTNER study was a study of HIV serodifferent couples (one HIV positive and one negative) to precisely estimate risk of within-couple transmission through sex where condoms not used, and in which the positive partner was on suppressive ART (HIV viral-load <200 copies/ml) **[R2]**. Phase 1 (PARTNER1), recruited both gay and heterosexual serodifferent couples from 2010 to 2014 and the second phase (PARTNER2) recruited gay serodifferent couples from 2014 to 2018.
PARTNER1 interim results were presented in 2014 at a major international conference (CROI) **[R3]** and final results were published in *JAMA* in 2016 **[R4]**. The results indicated that, among 548 serodifferent heterosexual and 340 gay couples, there were no documented cases of within-couple HIV transmission (determined by viral genetic linkage) despite 58,000 sex acts where condoms were not used. However, there was still not enough data from PARTNER1, in gay men

on suppressive ART, to be able to confidently say the risk was zero. The final results of PARTNER 2, presented at the World AIDS conference (AIDS2018) in July 2018 **[R5]** and published in *The Lancet* in 2019 **[R6]**, demonstrated that risk of HIV transmission through condomless anal sex with an undetectable viral load is zero, with no linked transmissions despite gay couples reporting 76,000 sex acts without using condoms. The results of PARTNER demonstrated zero risk applies in both heterosexual serodifferent couples (PARTNER1) and gay men (PARTNER2). The PARTNER studies were specifically designed to be large enough to make the upper 95% confidence interval risk negligible around the study finding of zero.

Alongside, Rodger and Phillips' modelling studies predicted that despite the majority of infections coming from HIV undiagnosed men, with substantial increases in testing and diagnosis rates and with immediate ART initiation at diagnosis, incidence of HIV would decline substantially. Such a policy was cost effective from a UK NHS perspective, with cost saving (if delivered at cost) below GBP8m **[R7]**.

In Altmetric scoring, PARTNER2 was in the top 100 (number 29) out of 2.7 million research outputs, indicating global influence and impact outside academic channels in 2019. PARTNER2 won the European Hector Research Award **(**2019**)** for most impactful HIV research in Europe and included by *BBC Science Focus* as one of the 'landmark scientific breakthroughs of 2019'.

3. References to the research

[R1] Rodger, A.J., Bruun, T., Vernazza, P., Collins, S., Estrada, V., Van Lunzen, J., Corbelli, G.M., **Phillips, A.N.,** Lundgren, J.D.; PARTNER Study Group. (2013). 'Further research needed to support a policy of antiretroviral therapy as an HIV prevention initiative'. *Antivir Ther.* **18**(3), 285-7. DOI: http://doi.org/10.3851/IMP2609.

[R2] Rodger, A., Bruun, T., Weait, M., Vernazza, P., Collins, S., Estrada, V., Lunzen, J.V., Corbelli, G.M., Lampe, F., **Phillips, A.**, Lundgren, J.; PARTNER study group. (2012). 'Partners of people on ART - a New Evaluation of the Risks (The PARTNER study): design and methods'. *BMC Public Health*. **12**, 296. DOI: http://doi.org/10.1186/1471-2458-12-296.

[R3] Rodger, A. et al. (2014). 'HIV transmission risk through condomless sex if HIV+ partner on suppressive ART: PARTNER study'. 21st Conference on Retroviruses and Opportunistic Infections (CROI), Late breaker conference presentation. Abstract 153LB, Boston, USA,. https://www.croiconference.org/abstract/hiv-transmission-risk-through-condomless-sex-if-hiv-partner-suppressive-art-partner-study/

[R4] Rodger, A.J., **Cambiano, V.**, Bruun, T., Vernazza, P., Collins, S., van Lunzen, J., Corbelli, G.M., Estrada, V., Geretti, A.M., Beloukas, A., Asboe, D., Viciana, P., Gutiérrez, F., Clotet, B., Pradier, C., Gerstoft, J., Weber, R., Westling, K., Wandeler, G., Prins, J.M., Rieger, A., Stoeckle, M., Kümmerle, T., Bini, T., Ammassari, A., **Gilson, R.**, Krznaric, I., Ristola, M., Zangerle, R., Handberg, P., Antela, A., Allan, S., **Phillips, A.N.**, Lundgren, J.; 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: The PARTNER STUDY'. *JAMA*. **316**, 171-181. DOI: http://doi.org/10.1001/jama.2016.5148.

[R5] Rodger, A., Cambiano, V., Bruun, T. et al. (2018). 'Risk of HIV transmission through condomless sex in gay couples with suppressive ART: the PARTNER2 study expanded results in gay men'. Abstract WEAX0104LB. 22nd International AIDS Conference. 23–27 July, 2018. Amsterdam, the Netherlands.

[R6] Rodger, A.J., Cambiano, V., Bruun, T., Vernazza, P., Collins, S., Degen, O., Corbelli, G.M., Estrada, V., Geretti, A.M., Beloukas, A., Raben, D., Coll, P., Antinori, A., Nwokolo, N., Rieger, A., Prins, J.M., Blaxhult, A., Weber, R., Van Eeden, A., Brockmeyer, N.H., Clarke, A., Del Romero, Guerrero J., Raffi, F., Bogner, J.R., Wandeler, G., Gerstoft, J., Gutiérrez, F., Brinkman, K., Kitchen, M., Ostergaard, L., Leon, A., Ristola, M., Jessen, H., Stellbrink, H.J.,

Phillips, A.N., Lundgren, J.; PARTNER Study Group. (2019). 'Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study'. *Lancet*. **393**(10189), 2428-2438. DOI: http://doi.org/10.1016/S0140-6736(19)30418-0 (Altmetric score measuring the impact of the PARTNER2 study is at https://www.altmetric.com/details/59839144)

[R7] Phillips, A.N., Cambiano, V., Miners, A. et al. (2015). 'Potential impact on HIV incidence of higher HIV testing rates and earlier antiretroviral therapy initiation in MSM'. *AIDS*, **29**(14), 1855-62. DOI: http://doi.org/10.1097/QAD.0000000000000767

4. Details of the impact

Informing global strategies and guidelines to end the HIV epidemic

Interim PARTNER1 data **[R3]** indicated that among 548 serodifferent heterosexual and 340 gay couples, there were no documented cases of within-couple HIV transmission despite 58,000 condomless sex acts. These results were shown to have an immediate global impact. These results were cited as evidence in the role of viral suppression via antiretroviral therapy (ART) in preventing HIV transmission in the UNAIDS 90-90-90 Strategy 'Ambitious Treatment Targets: Writing the Final Chapter of the Aids Epidemic (2017)', which aimed to have 90% of people living with HIV diagnosed, 90% on treatment and 90% living with viral suppression by 2020 **[S1]**. PARTNER was also a key evidence source (and the only data for gay men) in the 2016 World Health Organization Guidelines **[S2]** 'The Use of Antiretroviral Drugs for Treating and Preventing HIV', as the official recommendation for global public health approaches to HIV. Citing **[R3]** and **[R4]** as a key research findings within the report's clinical guidelines, the WHO recommended "*Initiating ART at any CD4 cell count[…]in order to reduce mortality, morbidity and HIV transmission outcomes […]substantially reducing transmission to HIV-negative sexual partners among homosexual couples",* reflecting the studies' findings and recommendations. In monitoring the implementation of these WHO HIV 'treat all (patients)' policies, low/middle-income countries adopting WHO guidance rose from 33% (2016) to 93% (2018) as the transmission benefits of ART demonstrated in the UCL research became official WHO policy **[S2]**.

In the UK, HIV positive gay men with an undetectable viral load increased from 48% in 2011 (pre-PARTNER1) to 87% in 2017 (post-PARTNER1) **[S3]**. Rodgers et al. estimated, through modelling, that the number of incident cases of HIV in England and Wales in men who have sex with men (MSM) fell 71% from 3,500 in 2015 to 800 in 2018 **[S3]**, demonstrating the significant reduction in HIV transmissions through universal roll-out of ART in policy and practice, which resulted in the large reduction in new UK infections in MSM. PARTNER1 has also been shown to alter treatment plans for those exposed to HIV. Based on **[R3]** and **[R4]**, findings in the absence of transmission in condomless acts between serodifferent partners, UK post-exposure prophylaxis for sexual exposure (PEPSE) guidelines were updated by the British Association for Sexual Health and HIV (BASHH) and the British HIV Association (BHIVA) in 2015. These guidelines recommended that Post-exposure prophylaxis (PEP) treatment was now not necessary, in the circumstances that the HIV positive person was known to be taking ART with a confirmed and sustained HIV viral load <200 copies/ml **[S3]**, switching from their previous recommendation to prescribe PEP. This would save their sexual partner potentially from having to take the 28-day treatment course of PEP, as well as the additional HIV testing and counselling.

National US HIV treatment guidelines were updated using both PARTNER 1 and PARTNER2 data in December 2019 by the US Department of Health and Human Services (DHHS) and National Institute of Health, who strongly recommend that: *"All PLWH should be informed that HIV viral load <200 copies/mL prevents sexual transmission of HIV*" **[S4]**. Based on these findings, the DHHS went on to make further recommendations that PLWH should use another form of prevention with sexual partners for at least six months from starting ART, until a viral load of <200 copies/mL has been documented, with patients explicitly told that by not adhering to ART, their viral load will increase rapidly and increasing their risk to transmission. DHHS also recommended further support through counselling should be given to maintain suppression through ART

adherence, which could be challenging for a number of social groups such as adolescents or homeless people.

Launched in 2019, PARTNER data also underpins the current US national HIV/AIDS strategy 'Ending the HIV Epidemic' **[S4]**, which aims to reduce new infections of HIV by 75% by 2025, and 90% by 2030. A 2019 position paper by the US Assistant Secretary for Health, Admiral Brett Giroir, entitled 'The Time is Now to End the HIV Epidemic', stated: "*recent data* **[R6]** *from multiple long-term, well-controlled studies have established that people with HIV who take HIV medication daily as prescribed, and maintain an undetectable viral load, have effectively zero risk of sexually transmitting HIV. The profound prevention benefit of treatment is the foundation for a community-led campaign known as Undetectable = Untransmittable (U = U), which is also a key strategic advantage for our initiative*". The level of confidence enabled by PARTNER 1 and PARTNER2 data - that taking ART daily maintains viral suppression and eliminates HIV sexual transmission - was also recognised by unprecedented changes in the US Centers for Disease Control and Prevention (CDC) recommendations (2019). After citing **[R4]** and **[R6]**, the CDC stated: "*ART is 100% effective to prevent sexual transmission in heterosexuals and gay men*" **[S4]** as part of a calculation of the effectiveness of prevention strategies for acquiring or transmitting HIV. As Dr Anthony Fauci, Director of the US National Institute for Allergy and Infectious Diseases stated at the 2019 International AIDS Society Conference on HIV Science: "*Treatment as Prevention, or U=U, is the hallmark of what we [NIAID] are doing…the concept of U=U is the foundation of being able to end the* epidemic" **[S4]**.

Addressing criminalisation of PLWH

Criminalizing PLWH undermines epidemic control efforts, promotes stigma, discourages testing and treatment and stigmatizes vulnerable populations. PARTNER results **[R4]** and **[R5]** underpin the International AIDS Society (IAS) consensus statement (2018), to combat criminalization laws that imprison hundreds of people based on assumptions of risk that the PARTNER results disprove. The Consensus statement extensively references PARTNER data, using UCL's up-to-date scientific evidence to limit unjust criminal prosecutions, calling for "*correct and complete understanding of current scientific knowledge to inform any application of the criminal law in cases related to HIV"* **[S5]**. PARTNER data has led to modernisation/repeal of HIV-specific laws, including in the US, Malawi, Canada, the DRC, Brazil and Belarus, as outlined in the HIV Justice Network report in 2019 **[S5]**.

Underpinning the U=U consensus statement

PARTNER data was pivotal for underpinning the definition of the 2016 treatment as prevention statement Undetectable=Untransmittable (U=U): *"A person living with HIV who has undetectable viral load does not transmit HIV to their partners"* **[S6]**. In 2016, the founder of U=U, health equality initiative Prevention Access, contacted the PARTNER study group about transmission risks of HIV, looking to use data to transform the social, sexual, and reproductive lives of PLWH. Together with multiple citations from NAM (AIDS charity) AidsMap, the organisations utilised the UCL groups' research to cement the message that HIV is not transmittable with viral suppression on ART. After this, 'U=U' was launched. Advocating for favourable health outcomes, including ART adherence, optimal health and disclosure of HIV status, the influential U=U statement was initiated following PARTNER1 interim results **[R3]** and publication **[R4]**, and is now endorsed by >1000 organisations in 100 countries, including Elton John Aids Foundation and the Africa Centre for Health Policy **[S6]**.

The effect of the PARTNER studies are felt across the landscape of health service users - from policy makers to PLWH. PARTNER research has also helped fight stigma that is repeatedly recognized as a major barrier to HIV testing and treatment, providing the scientific evidence to place U=U at the heart of HIV prevention policy and efforts to destigmatise HIV. This effort was summed up by one PLWH in 2018, who said: "*It was like the sky opened. There's, like, zero risk? I don't feel I'm a threat anymore. I don't feel I'm dirty. I don't feel I'm dangerous*." **[S7]**

In 2018, PARTNER2 results **[R5]**, **[R6]**, finally provided scientific evidence for transmission risk of zero with suppressive ART in gay men. The author of the U=U, Bruce Richman, stated:

"Something shifted in 2018. We're tremendously grateful to the groundbreaking PARTNER2 researchers for the unequivocal final chapter confirming U=U. PARTNER2 has forever changed what it means to live and love with HIV around the world" **[S8]**. The PARTNER study team has always engaged with the HIV community to help rapid dissemination and trust in study results: Bruce Richman said, in 2018: "*Alison Rodger did something so unusual and wonderful, she confirmed the research supports U=U and acknowledged Prevention Access Campaign for our work to ensure evidence reaches the public. It was so respectful. I'm so grateful to her.*" **[S8]** Matthew Hodson (Executive Director of AIDSMAP), commented on the confidence PARTNER2 data gave the U=U movement: "*IAS2018 will forever be remembered as the conference when 'U=U' moved from an activist rallying cry to the scientifically established position."* **[S8]**

5. Sources to corroborate the impact

[S1] UNAIDS Ambitious Treatment Targets: Writing the Final Chapter of the AIDS Epidemic (p.3)

[S2] 2016 WHO Guidelines: The Use of Antiretroviral Drugs for Treating and Preventing HIV: Recommendations for a public health approach (2nd Edition, Chapter 4; p75); 2019 WHO HIV Policy Adoption and Implementation Status in Countries (Pdf).

[S3] PHE (2019) 'HIV in the United Kingdom: Towards Zero HIV transmissions by 2030' (p8, p69).https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/858559/HIV_in_the_UK_2019_towards_zero_HIV_transmissions_by_2030.pdf; BHIVA 2015 PEPSE guidelines: https://www.bhiva.org/PEPSE-guidelines (p16).

[S4] National U.S. Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in Adults & Adolescents w/ HIV December, 2019 (p. 2). US national HIV/AIDS strategy, Ending the HIV Epidemic in the U.S); https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6893354/ ; CDC (July 2019). Effectiveness of Prevention Strategies to Reduce the Risk of Acquiring or Transmitting HIV. Dr Anthony Fauci NIAID Treatment as Prevention plans

[S5] JAIS (2018). Expert consensus statement on the science of HIV in the context of criminal law. https://onlinelibrary.wiley.com/doi/full/10.1002/jia2.25161#; HIV Justice: https://www.hivjusticeworldwide.org/en/milestones/ and *Advancing HIV Justice 3: Growing the global movement against HIV criminalisation*. HIV Justice Network, Amsterdam, May 2019.

[S6] Prevention access https://www.preventionaccess.org/consensus and Prevention Access Campaign. About, 2017. Available: https://www.preventionaccess.org/about [Accessed 04 September 2020]; Okoli C, Van de Velde N, Richman B*, et al* Undetectable equals untransmittable (U = U): awareness and associations with health outcomes among people living with HIV in 25 countries. *Sexually Transmitted Infections.* Published Online First: 30 July 2020. doi:10.1136/sextrans-2020-054551

[S7] PLWH response to U=U. Jennifer Vaughan, in Washington Post including video describing the impacts of the PARTNER1 study and U=U https://www.washingtonpost.com/national/health-science/i-dont-feel-like-im-a-threat-anymore-new-hiv-guidelines-are-changing-lives/2017/11/24/a9ee84e2-cf10-11e7-a1a3-0d1e45a6de3d_story.html

[S8] Bruce Richman (CEO Prevention Access) Tweet 24 December 2019 (Pdf); https://www.hivplusmag.com/stigma/2020/1/27/bruce-richman-meet-man-behind-uu; Report in Americas AIDS Magazine (community publication) on the impact of PARTNER results with quotes from Bruce Richman and Matthew Hodson, the Executive Director of NAM aidsmap https://aumag.org/2018/08/07/partner2-study-confirms-undetectable-equals-untransmittable/