Celebrating HIV research

Retirement celebrations for Professors Kholoud Porter, David Dunn and Sheena McCormack



1 May 2025, Denys Holland Lecture Theatre

Simon Collins, HIV i-Base
www.i-Base.info

Disclosure

Thank you - I am proud to have been asked to give this talk.

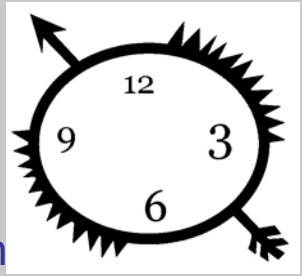
Celebrating over 90 years!

Kholoud Porter

David Dunn

Sheena McCormack

Community and research timeline



1981 – 1987: 8 years to manage OIs, stigma and hope.

1987 – 1995: Old compounds as single drug monotherapy.

AZT (1987), ddI (1991), ddC (1992), d4T (1994), 3TC (1995)

1996 - 2002: New drugs (NNRTIs and PIs) in triple combination

Viral load PCR monitoring and drug resistance tests.

20+ daily pills, side effects and drug resistance.

2000 onwards: Global access. Single pills. Generics. PEPFAR.

2002 – 2014: New NNRTIs & PIs. Inflammation. INSTI class. Early PrEP.

2015 – 2025: PROUD, PARTNER, START, U=U and many more.

OIs opportunistic infections, U=U: undectectable = untransmissible.

Key studies

MRC and UCL studies were partnerships both in the UK and internationally. Collaborations last for decades.

- Concorde and Delta virology
- UK Seroconvertor Cohort and CASCADE
- UK HIV Drug Resistance Database
- PROUD study
- PARTNER and U=U (Undetectable = Untransmissible)
- START for universal ART

Concorde (AZT)

- Oct 1988 to Oct 1991: Randomised 1749 asymptomatic people living with HIV to immediate or deferred AZT (250 mg QID), follow-up to end 1992 or death.
- Roughly half the deferred group started AZT due to AIDS or CD4 <500.
- High exposure to AZT led to no significant clinical differences including 3-year survival (p=0.13), progression to AIDS (p=0.18) or deaths compared to placebo.
- Median CD4 was higher at 6 months with AZT (+50 vs –50 cells) and then steadily dropped in both groups.

Ref: *Lancet.* 1994; 343:871-881.

Concorde (AZT)

Results April 1993, published April 1994.

I remember where I was when the news broke.

CONCORDE was controversial (dosing, toxicity, pricing) but it led with new data and longer-term results.

Rapid early approval, early resistance and limited benefit in advanced HIV.

But it was all there was.

BMJ 19 June 1993

Criticisms of Concorde dominate AIDS conference

The Concorde study, the most comprehensive drug trial in the history of research on AIDS, was put on trial itself at last week's international conference on AIDS in Berlin. By the end of the week, however, there was still no verdict.

The Anglo-French trial recruited 1749 people who were infected with HIV but were asymptomatic and followed them up over three years. The trial was designed to see whether early treatment with zidovudine would prolong life. Earlier American studies had suggested that the drug could delay the onset of AIDS.

The trial randomised people to receive either the drug or a placebo. Any person who became unwell was given zidovudine. The protocol was changed a year after the study began after results from an American trial indicated that people would benefit from zidovudine when their CD4 counts fell to below 500×10^6 cells/l.

At a plenary session Professor Maxime Seligmann, an immunologist and one of Concorde's principal researchers, said that the trial's preliminary findings, which were published in a letter in the *Lancet* on 3 April, had been backed up by further analysis. In particular, there was no difference between the two groups in survival rates or progression to AIDS.

CD4 counts rose initially in patients given zidovudine but then fell parallel to the counts in those who were not given the drug. The study's other main finding was the low rate of adverse effects of zidovudine.

But the study was criticised even before most of the 13 000 delegates reached Berlin. In a symposium held the day before the

Concorde has cast doubts on the place of Zidovudine in asymptomatic HIV infection

HANK MORGANSTEIN

the American trials.

The first American trial was of 282 patients who already had AIDS and was published in 1987. Zidovudine decreased mortality and reduced opportunistic infections. The second trial was of 1338 patients with CD4 counts below 500×10^6 cells/l. Two thirds of the patients received zidovudine and one third received a placebo. The results showed a

now was to prescribe zidovudine when any symptoms of immunodeficiency developed, when CD4 counts fell below 200×10^6 cells/l, or when the CD4 count fell suddenly from a somewhat higher level.

Numerous speakers joined the Concorde team in expressing doubt over the use of clinical markers such as CD4 counts. Most admitted that no better marker of progres-

Delta study – and virology

AZT vs AZT+ddI vs AZT+ddC

DELTA was an RCT in >3200 people with symptoms or CC4 <350. One-third were pretreated. [1]

Showed benefits of dual therapy in people who hadn't used AZT before. Adding ddI but not ddC also improved survival.

Over 30 months, 699 people died.

An extended virology substudy provided the data to support wider use and confidence in the importance of viral load. [2]

1. *Lancet.* 1996; 348:283-291

2. *AIDS* 13(1):p 57-65, January 14, 1999.

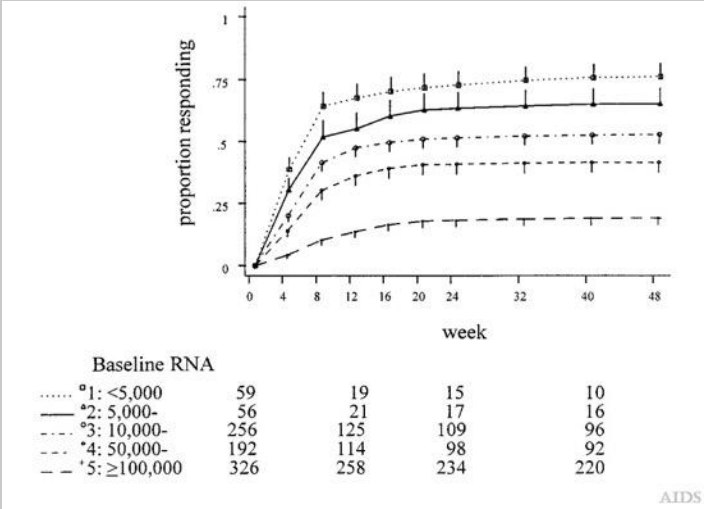
Delta virology

>1200 participants (>9400 samples) helped validate viral load as a surrogate endpoint.

Baseline, weeks 4, 8, 12, 16, 20, 24 and every 8 weeks to week 64. Stored –70 C, viral load test with cut-off <800 c/mL.

Baseline viral load independently predicted outcomes including mortality, nadir and risk of viral rebound.

Ongoing viral load informing when to change ART etc.



HIV-1 RNA response to antiretroviral treatment in 1280 participants in the Delta Trial: an extended virology study. AIDS. 1999 Jan 14;13(1):57-65.

Community and research

1983 - Denver Principles included active involvement of people living with HIV in all aspects of our care, including research.

1987 - Act-UP challenged structure of drug research, development and approval.

UK studies since CONCORDE all involved community with

PROUD had a community co-chair, and community reps were on steering and management cttees and DSMBs.

Research and community

- UK studies have always had community links.
- Ideally, this includes at planning stages, protocol and participant information. Community can help a study enrol more quickly and to publicise results.
- Janet Darbyshire and Tim Peto were involved with the first UK-CAB meeting in 2002.
- UK-CAB connects over 700 community advocates and reps are included on all UK guidelines and phase 3 studies.

Professor Janet Darbyshire and Professor Tim Peto

UK register of seroconvertors

Set up in 1994 to study the natural history of HIV.

A collaboration with >100 clinical centres and 3500 participants. Also linked surveillance data and clinical trials.

The cohort joined the international CASCADE study that connects a large network of research cohorts across Europe.

A unique data set that still continues to inform our understanding of the natural history of HIV and the complex questions about the impact of HIV and treatment.

Now part of the HIV research at the Institute of Global Health.

CASCADE

Collaboration with 9 other European countries and Australia. Includes >8700 seroconverters from 19 studies.

CASCADE workshop, Barcelona, 2009.

Data on natural history, drug resistance, weight changes and impact of ART etc with at least 50 published studies.

Can separate out the impact of HIV when minimal return to health impact.

Also on the role of nadir CD4 count after interrupting ART.

CASCADE

Differences in HIV RNA levels before the initiation of antiretroviral therapy among 1864 individuals with known HIV-1 seroconversion dates

AIDS 2004, Natural history and lower viral load in women.

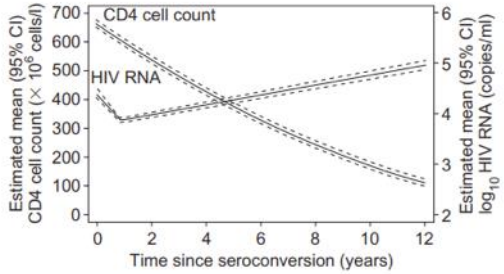


Fig. 1. Estimated average CD4 cell counts (× 10^6/l) and HIV RNA (log_{10} copies/ml) trajectories by time since seroconversion.

> AIDS. 2013 Sep 24;27(15):2451-60. doi: 10.1097/01.aids.0000431945.72365.01.

Natural history of HIV-control since seroconversion

Yoann Madec [1], Faroudy Boufassa, Kholoud Porter, Maria Prins, Caroline Sabin, Antonella d'Arminio Monforte, Pauli Amornkul, Barbara Bartmeyer, Mette Sannes, Alain Venet, Olivier Lambotte, Laurence Meyer; CASCADE Collaboration in Eurocoord

Collaborators, Affiliations + expand

PMID: 23912979 DOI: 10.1097/01.aids.0000431945.72365.01

AIDS 2013, Natural history of HIV control

CASCADE

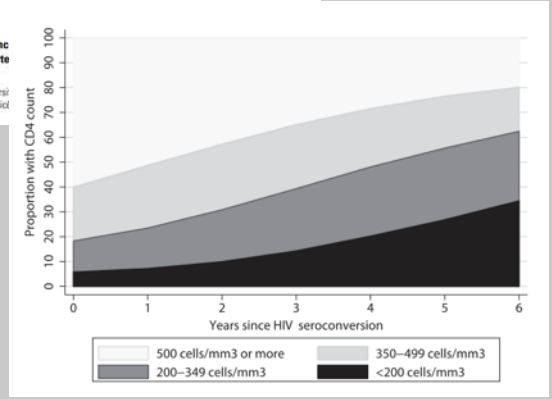
THE LANCET HIV

MAJOR ARTICLE HIV/AIDS

Time From Human Immunodeficiency Virus Seroconversion to Reaching CD4+ Cell Count Thresholds <200, <350, and <500 Cells/mm^3: Assessment of Need Following Changes in Treatment Guidelines

Sara Lodi,[1] Andrew Phillips,[2] Giota Touloumi,[3] Ronald Geskus,[4] Laurenc
Julia del Amo,[7] Anne M. Johnson,[2] Abdel Babiker,[1] and Kholoud Porte
EuroCoord[a]

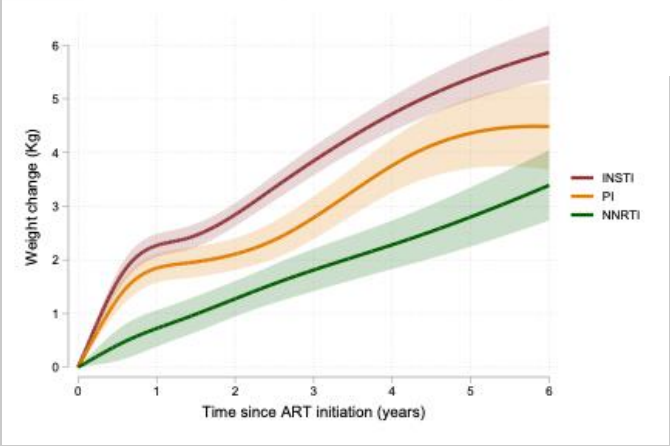
[1]MRC Clinical Trials Unit, [2]University College London, United Kingdom; [3]Athens Universi
Academic Medical Centre, the Netherlands; [5]Paris Sud 11/INSERM U1018, le Kremlin Bicl
de Salud Carlos III, Madrid, Spain



CID 2011 Time to CD4 thresholds

Changes in bodyweight after initiating antiretroviral therapy close to HIV-1 seroconversion: an international cohort collaboration

Nikos Pantazis, PhD [a] · Prof Caroline A Sabin, PhD [b] ·



Lancet HIV 2024 weight gain

UK resistance database

- Launched in 2001 as a UK database and network and included community.
- Supported by the NHS, Dept of Health, MRC, CHIVC and industry at different times.
- Changing technology and complex interpretation of results. We needed labs to collaborate on questions that small datasets couldn't answer.
- Issues about confidentiality over transmissions and criminalisation.

UK resistance database

Surveillance data showed transmitted drug resistance was linked to early ART era.

Antiretroviral Drug Resistance in HIV-1-Infected Patients with Low-Level Viremia

Nicola E. Mackie,[1] Andrew N. Phillips,[2] Steve Kaye,[1] Clare Booth,[3] and Anna-Maria Geretti,[2,3] on behalf of the UK Resistance Database and the UK Collaborative HIV Cohort Study

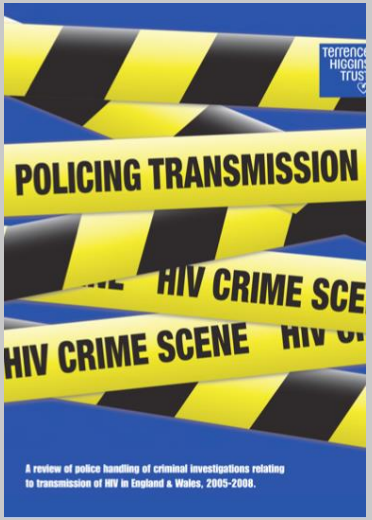
THE LANCET HIV

Lancet HIV, 2019

Mosaic effectiveness: measuring the impact of novel PrEP methods

Prof David V Glidden, PhD [a] · Megha L Mehrotra, MPH [a] · Prof David T Dunn, PhD [c] · Elvin H Geng, MD [b]

Affiliations & Notes Article Info



THT report on criminalisation of transmission

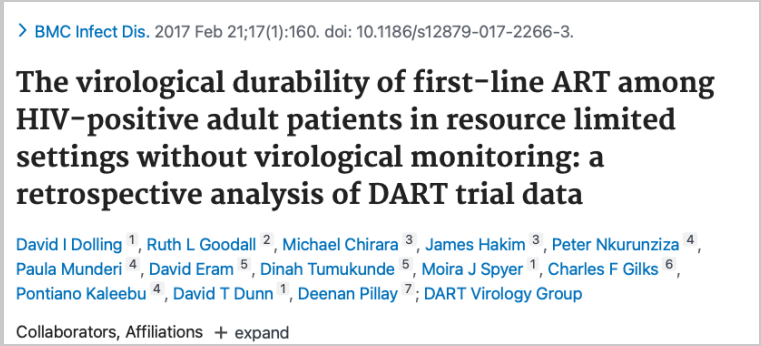
UK resistance database

Randomized Controlled Trial · J Acquir Immune Defic Syndr. 2025 Mar 1;98(3):274-281. doi: 10.1097/QAI.0000000000003564. Epub 2025 Feb 5.

Assessing Whether Providing Regular, Free HIV Self-Testing Kits Reduces the Time to HIV Diagnosis: An Internet-Based, Randomized Controlled Trial in Men Who Have Sex With Men

David T Dunn [1], Leanne McCabe [1], Denise Ward [1], Andrew N Phillips [2], Fiona C Lampe [2], Fiona Burns [2], Valerie Delpech [3], Peter Weatherburn [4], T Charles Witzel [2], Roger Pebody [5], Peter Kirwan [3], Jameel Khawam [3], Sara Croxford [3], Michael Brady [6], Kevin A Fenton [7], Roy Trevelion [8], Yolanda Collaco-Moraes [1], Sheena McCormack [1], Alison J Rodger [2]

JAIDS 2025



BMC Infect Dis. 2017 Feb 21;17(1):160. doi: 10.1186/s12879-017-2266-3.

The virological durability of first-line ART among HIV-positive adult patients in resource limited settings without virological monitoring: a retrospective analysis of DART trial data

David I Dolling [1], Ruth L Goodall [2], Michael Chirara [3], James Hakim [3], Peter Nkurunziza [4], Paula Munderi [4], David Eram [5], Dinah Tumukunde [5], Moira J Spyer [1], Charles F Gilks [6], Pontiano Kaleebu [4], David T Dunn [1], Deenan Pillay [7]; DART Virology Group

Collaborators, Affiliations + expand

BMC Infect Dis 2017

AIDS. 2015 Sep 24;29(15):1917-25. doi: 10.1097/QAD.0000000000000768.

A phylotype-based analysis highlights the role of drug-naive HIV-positive individuals in the transmission of antiretroviral resistance in the UK

Raphaël Mourad [1], François Chevennet, David T Dunn, Esther Fearnhill, Valerie Delpech, David Asboe, Olivier Gascuel, Stéphane Hue;
UK HIV Drug Resistance Database & the Collaborative HIV, Anti-HIV Drug Resistance Network

AIDS 2015

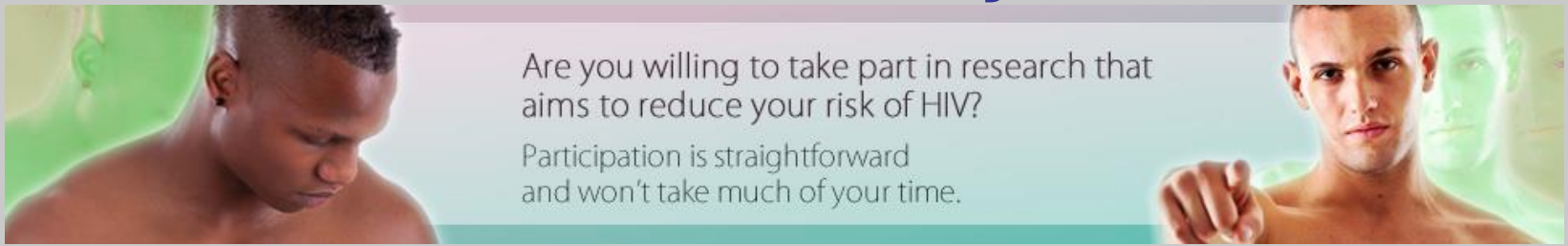
MDP and early HIV vaccine work

Microbicides Development Programme (MDP)

Founded in 2000 and funded by DfID. Included phase 3 study of PRO2000 microbicide in sub-Saharan Africa.

Lancet. **376** (9749): 1329–37.

PROUD study



2012 – TDF/FTC approved as oral PrEP in the US.

2012 – UK plans PROUD: immediate vs deferred PrEP, starting as a pilot study.

Nov 2012 – Apr 2014 enrolled. Decided on a need for a DSMB in January 2014.

October 2014 – stopped early by DSMB - significant benefits.

Feb 2015 – results presented at CROI.

October 2015 – published open-access in the Lancet.

The Lancet. Sept 9 2015.

PROUD study

- Community involved at all levels.
- Community co-chair, protocol input and participant info.
- Included in Steering and Management Cttees and the DSMB. Ran participant meetings.
- No PrEP in the UK so included deferred access design – no placebo.

So effectively enrolled men at risk that the pilot study became powered to prove efficacy.

Adherence support with pill boxes.

Post -PROUD

- PROUD was the easy part.
- NHS refused to commission.
- NAT court case.
- PrEP 17 video – The coming of age of PrEP by Nicholas Feustel with Prepster
- Community talks and protests.
- 2020 - PrEP finally commissioned by NHS England following PrEP Impact trial.

NHS demo Jan 2015

https://prepster.info/prep17

PrEP, PARTNER, START and U=U

PrEP and PARTNER studies normalised HIV prevention.

Both effectively reduce risk >99%.

START enabled universal access to ART by producing data supporting clinical benefit at high CD4.

If someone tests positive, they can start ART – one pill a day and partners are protected too.

Continued drug development has led to long-acting ART and PrEP: access and pricing issues continue.

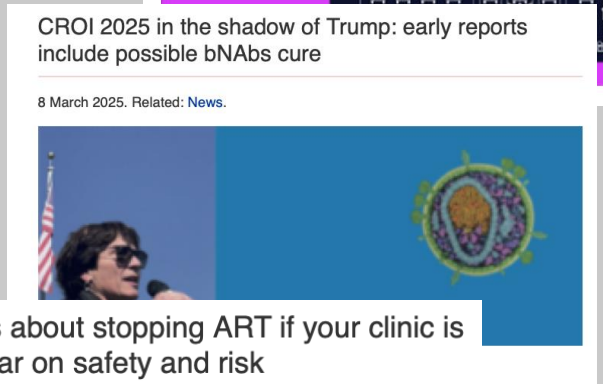
2025 update

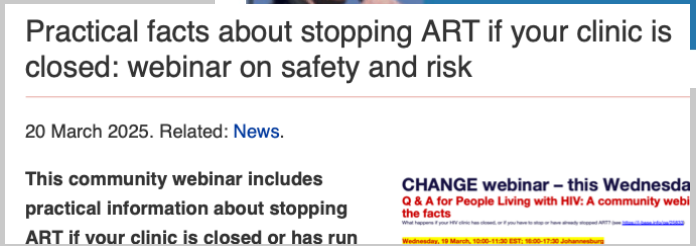
Since 20 January....

Decades of research are being dismantled.

Thousands of research studies and health clinics have been cancelled or closed.

Assaults to key populations take us back to the 1980s.





Recent news from i-Base, 2025

Imagine, if overnight…

All UK sexual health clinics closed.

Or we ran out of medicines.

Or 6000 research studies shut.

Or you were criminalised as LGBT people were in Uganda two years ago.

Or you were prevented from having a passport in the US or access treatment in the UK.

Moving to the future

20 million people are on single-pill ART and U=U also normalises living with HIV.

But the current US assault on science and public health is already undoing decades of progress.

So now we have new challenges.

New collaborations will be needed to protect the world we worked to hard to achieve.

Everyone can be involved.

Thank you

Thanks to Kholoud, David and Sheena for comments and to the MRC, UCL, IGH and ICTM for supporting national and international research.

Thanks to the UK-CAB for their network for community treatment advocacy.