

The History of Pharmacology at the University of Liverpool

(With a particular focus on Infection Pharmacology.)



David Back

25th International Workshop on Clinical Pharmacology of HIV, Hepatitis and Other Antiviral Drugs.

September 18th, 2024.



1

The PAST

2

The PRESENT



- ❑ Liverpool University was founded as a college in 1881.
- ❑ The Victoria Building (centrepiece of University) opened in 1892.
- ❑ University receiving a Royal Charter to award degrees in 1903.

- ❑ Liverpool Royal Infirmary opened in 1889 with training of medical students.
- ❑ Medical degrees awarded by the University of Manchester until 1903



- ❑ The Liverpool School of Tropical Medicine was founded in 1899.
- ❑ Initially shared premises with the University but moved to its own building in 1920.
- ❑ 1902: Ronald Ross was first British recipient of Nobel Prize for Medicine; transmission of malaria.



- ❑ 2001: New Build funded by Gates foundation.
- ❑ 2024: 510 Staff.
- ❑ Kevin de Cock – an alumni of the School



- ❑ **1920: Walter J Dilling** appointed as the first Lecturer in Pharmacology in the Medical School.
- ❑ **1930:** Appointed as the first Professor of Pharmacology and General Therapeutics. Died in **1950** (aged 64).
- ❑ Edited a textbook of Materia Medica which became **Dilling's Clinical Pharmacology**. First time the term Clinical Pharmacology used in any textbook.

BMJ March 31st, 1928.

**GANGRENE FOLLOWING THE USE OF
ERGOTIZED RYE BREAD.**

BY

**WALTER J. DILLING, M.B., CH.B.,
ASSOCIATE PROFESSOR OF PHARMACOLOGY, UNIVERSITY OF LIVERPOOL,**

AND

**R. E. KELLY, C.B., M.D., B.Sc., F.R.C.S.,
PROFESSOR OF SURGERY, UNIVERSITY OF LIVERPOOL.**

Case Report of Fungal Infection



- **1951-1974: Andrew Wilson** appointed Head of Department of Pharmacology & Therapeutics.
- Major interest was neuromuscular blockade and the disease of *Myasthenia gravis* (Muscle weakness).

Br. J. Pharmac. Chemother. (1966), 28, 348-359.

THE BILIARY EXCRETION OF NEOSTIGMINE
IN THE RAT

BY

T. N. CALVEY

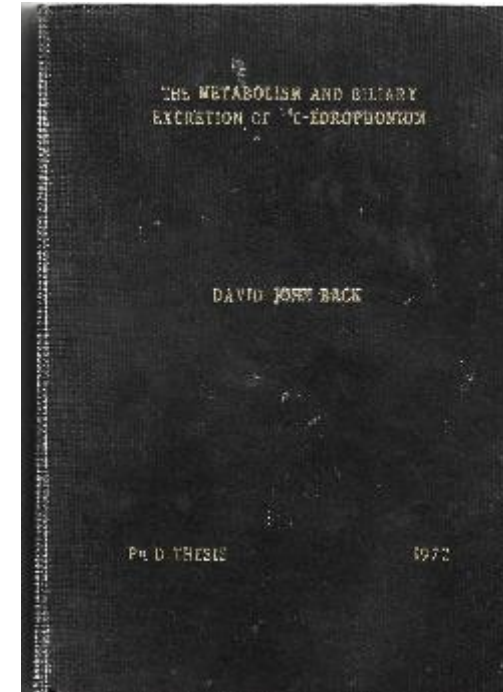
From the Department of Pharmacology and General Therapeutics, University of Liverpool

Br. J. Pharmac. (1972), **44**, 534–543.

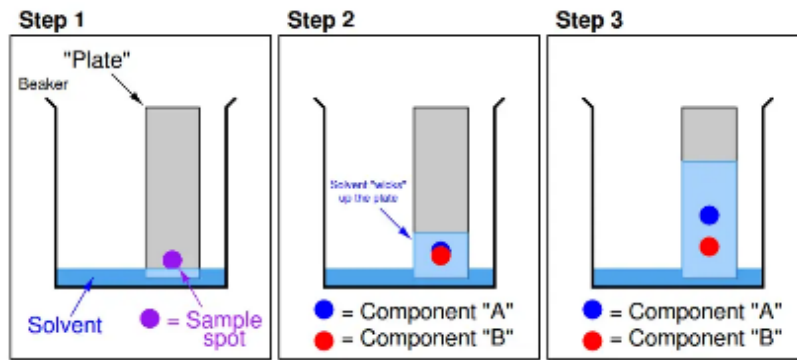
Excretion of ^{14}C -edrophonium and its metabolites in bile: role of the liver cell and the peribiliary vascular plexus

D. J. BACK AND T. N. CALVEY

*Department of Pharmacology and General Therapeutics, University of Liverpool,
Liverpool L69 3BX*



Thin-layer chromatography



Academic Staff - Department of Pharmacology & Therapeutics 1974



Note:

- All male staff.....
wearing ties!
- First female member
of staff, 1978.
- 9 Postgraduate
students.
- Andrew Wilson died
the day after retiring
(Sept 1974)



Professor Sir Alasdair Breckenridge

*Physician
Scientist
Educator
Regulator
Mentor*

- ❑ **1975: Professor Alasdair Breckenridge** appointed as Head of Department.
- ❑ Start of expansion.
- ❑ **1985:** 17 Academic staff, 18 post-graduate students.
- ❑ **2000:** Alasdair stood down as HOD. 25 Academic staff, 30 postgrads.

- ❑ **Sept 2024:** 50 Academic staff, 40 Postdocs, 25 Research Fellows/Associates, 100+ postgraduate students. Total departmental personnel ~225

Eur J Clin Pharmacol 1979; 15: 193-197.

The Effect of Rifampicin on Norethisterone Pharmacokinetics

D. J. Back, A. M. Breckenridge, Francesca Crawford, M. MacIver, M. L'E. Orme, B. K. Park, P. H. Rowe, and Eileen Smith

Department of Pharmacology and Therapeutics, University of Liverpool, England

- Female patients receiving RIF for TB. Single dose NET.
- Marked effect on NET PK with implications for contraceptive effectiveness

- Between 1979 and 1998, >60 papers on PK and DDI of Oral Contraceptives

The Past: 40+ Years of HIV:

Dec 1981: First UK case of an 'AIDS-related illness', reported.

July 1982: Death of Terence Higgins; one of the first to die from the new disease.

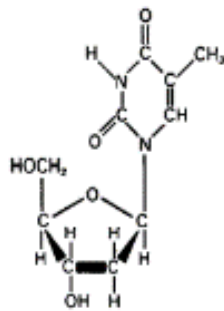


April 1987: Princess Diana opened the UK's first unit for HIV/AIDS patients at London Middlesex Hospital

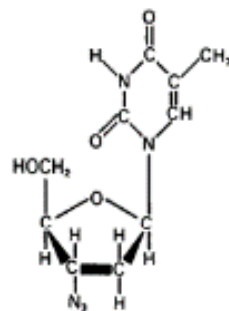


40+ Years of HIV: 1987 - The First Drugs

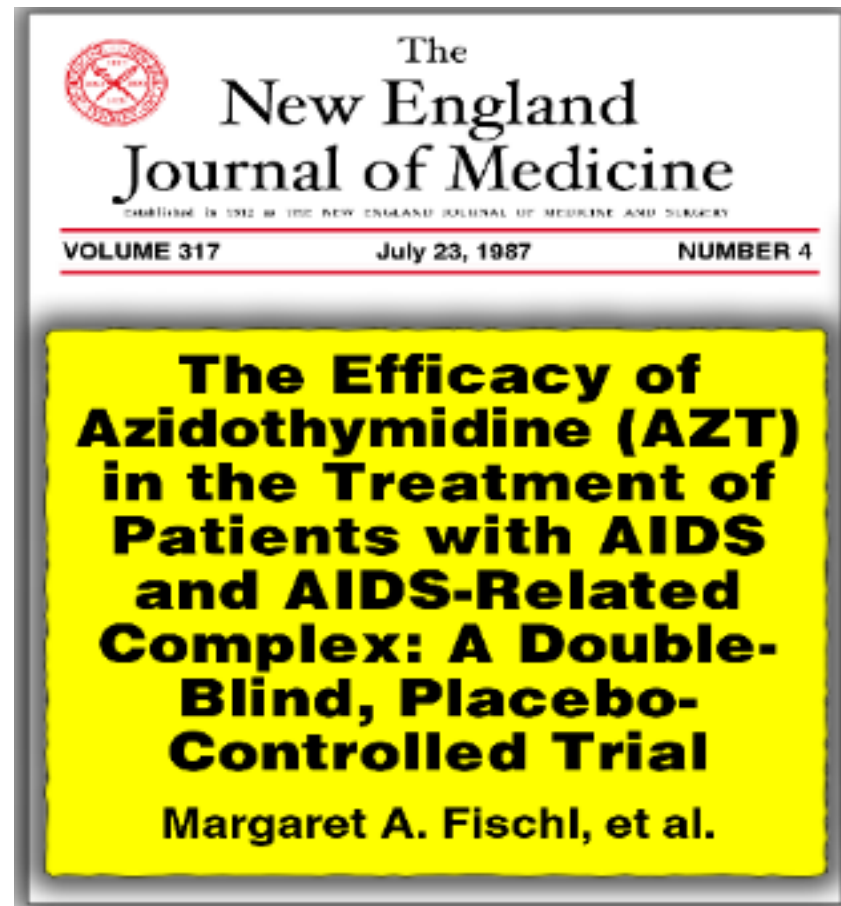
AZT was approved by the FDA as the first 'AIDS medication' on March 19, 1987, in a then record 20 months.

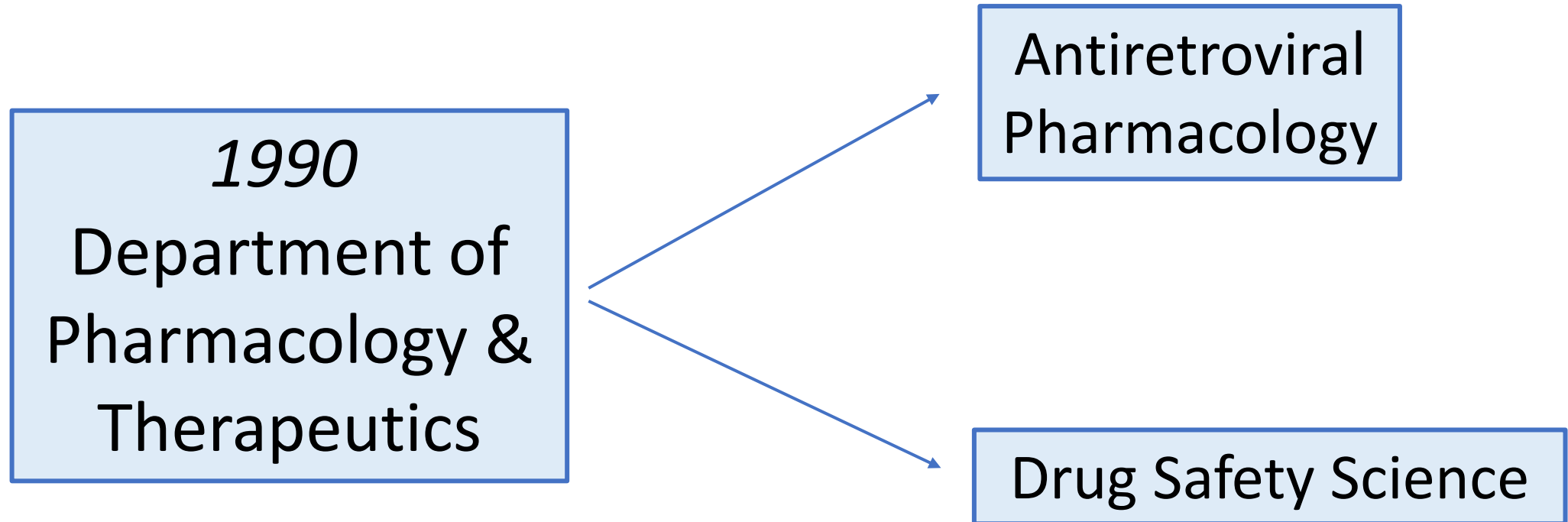


Thymidine



3'-Azido-3'-deoxythymidine (AZT)





THE LANCET

Articles

Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection

*Concorde Coordinating Committee**

- UK and France trial
- UK Chair – Alasdair Breckenridge

THE LANCET

Articles

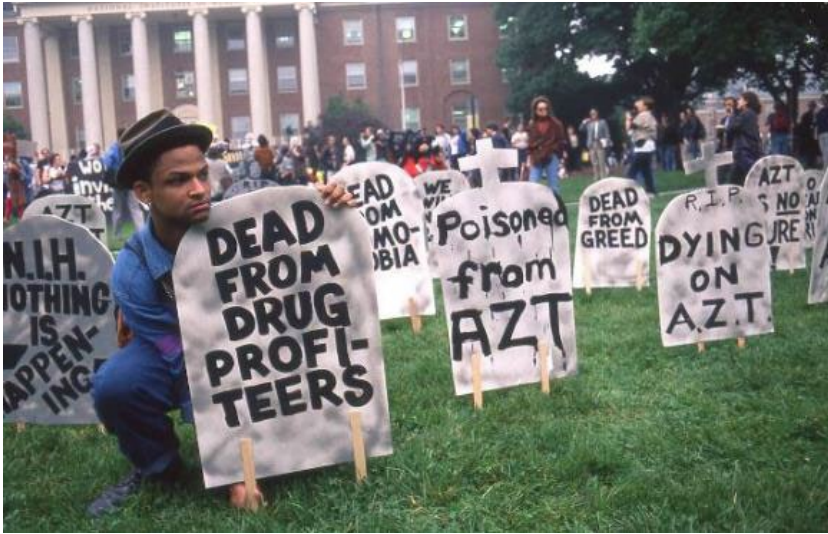
Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals

*Delta Coordinating Committee**

- UK, Australia, France, Italy trial
- UK Chair – Alasdair Breckenridge

- PK support – mainly adherence.

40+ Years of HIV: The Controversies



Current Medical Research and Opinion, Vol. 15, Suppl 1, 1999
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A Critical Analysis of the Pharmacology of AZT and its Use in AIDS

Eleni Papadopulos-Eleopulos¹, Valendar F. Turner²,
John M. Papadimitriou³, David Causer⁴, Helman Alphonso⁵
and Todd Miller⁶

From the evidence published it has become apparent that no phosphorylation takes place and thus AZT cannot possess any anti-HIV activity. It is difficult if not impossible to explain why AZT was introduced.

IN THE HIGH COURT OF SOUTH AFRICA
(NATAL PROVINCIAL DIVISION)

DAY OF JULY 2001

Case No: 1894/2001

In the matter between:

ANNET HAYMAN First Plaintiff
ANNET HAYMAN obo DAVID HAYMAN Second Plaintiff

and

GLAXO WELLCOME SOUTH AFRICA (PTY) LTD First Defendant
t/a **GLAXOSMITHKLINE**
THABO MBEKI Second Defendant
DR MANTO TSHABALALA-MSIMANG Third Defendant
PROFESSOR PETER EAGLES Fourth Defendant

FIRST DEFENDANT'S NOTICE – RULE 36(9)
PROFESSOR DAVID BACK

40+ Years of HIV: The Liverpool Connection

Br. J. clin. Pharmac. (1991), **32**, 17–21

ADONIS 030652519100133C

The effect of various drugs on the glucuronidation of zidovudine (azidothymidine; AZT) by human liver microsomes

S. M. SIM¹, D. J. BACK² & A. M. BRECKENRIDGE²

¹Department of Pharmacology, University of Malaya, Kuala Lumpur, Malaysia and ²Department of Pharmacology and Therapeutics, University of Liverpool, P.O. Box 147, Liverpool L69 3BX

- ❑ Human livers obtained in collaboration with the Royal Liverpool Hospital transplant unit.
- ❑ Bank of ~50 livers.

Br J clin Pharmac 1993; **36**: 82–85

The effects of indomethacin and naproxen on zidovudine pharmacokinetics

M. BARRY¹, J. HOWE¹, D. BACK¹, A. BRECKENRIDGE¹, R. BRETTE², R. MITCHELL², N. J. BEECHING³ & F. J. NYE³

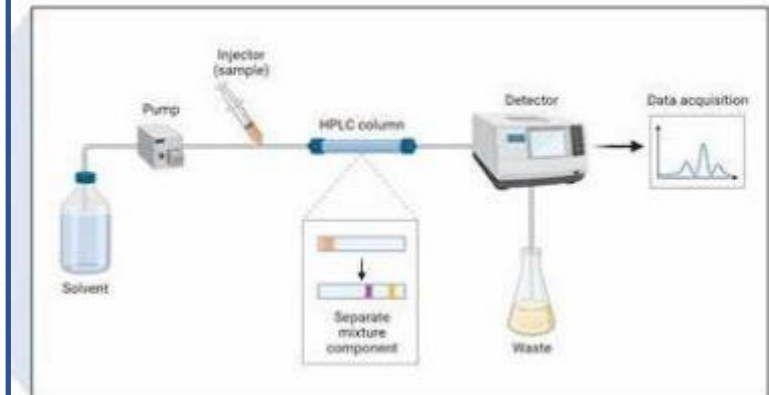
¹Department of Pharmacology and Therapeutics, University of Liverpool, ²City Hospital, Edinburgh and ³Regional Infectious Diseases Unit, Fazakerley Hospital, Liverpool



Initiated the first Clinical Research Facility

6 HIV+ patients

High Performance Liquid Chromatography (HPLC)



1994



FAST TRACK

AIDS 1997, 11:F29-F33

Saquinavir pharmacokinetics alone and in combination with ritonavir in HIV-infected patients

Concepta Merry^{*†}, Michael G. Barry^{*}, Fiona Mulcahy[†],
Mairin Ryan[†], Jane Heavey[†], John F. Tjia^{*}, Sara E. Gibbons^{*},
Alasdair M. Breckenridge^{*} and David J. Back^{*}

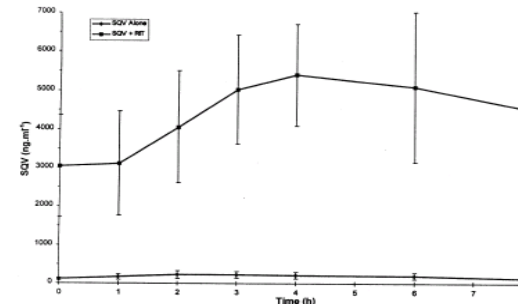


Fig. 2. Mean (\pm SEM) plasma saquinavir (SQV) steady state concentrations following treatment with SQV 600 mg three times daily alone and in combination with ritonavir (RIT) 300 mg twice daily.

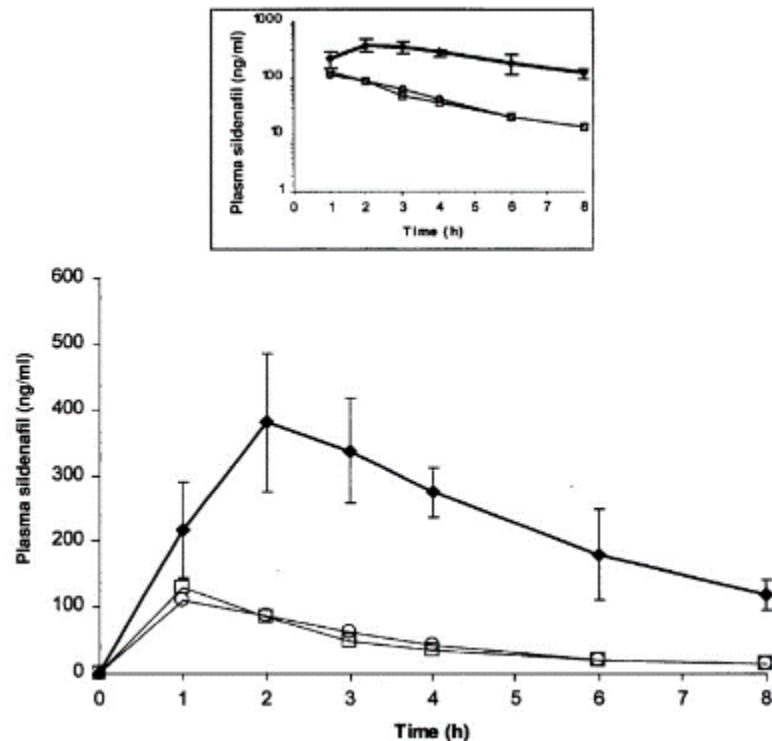
Pharmacokinetic Enhancement of Inhibitors of the Human Immunodeficiency Virus Protease by Coadministration with Ritonavir

DALE J. KEMPF,^{1*} KENNAN C. MARSH,² GONDI KUMAR,³ A. DAVID RODRIGUES,³
JON F. DENISSEN,³ EDITH McDONALD,² MICHAEL J. KUKULKA,³ ANN HSU,⁴
G. RICHARD GRANNEMAN,⁴ PAOLO A. BAROLDI,⁵ EUGENE SUN,⁶
DAVID PIZZUTI,⁶ JACOB J. PLATTNER,¹ DANIEL W. NORBECK,¹
AND JOHN M. LEONARD⁶

Departments of Infectious Diseases Research,¹ Drug Analysis,² Biotransformation,³ Pharmacokinetics,⁴
Clinical Pharmacology,⁵ and Antiviral Venture,⁶ Pharmaceutical Products Division,
Abbott Laboratories, Abbott Park, Illinois 60064

Interaction of sildenafil and indinavir when co-administered to HIV-positive patients

Concepta Merry^a, Michael G. Barry^a, Mairin Ryan^a, John F. Tjia^b,
Martina Hennessy^a, Victoria A. Eagling^b, Fiona Mulcahy^c
and David J. Back^b



Interestingly, two of the six patients reported pharmacodynamic effects of sildenafil up to 72 h after ingestion of a single dose. However, it is difficult to explain this observation solely on the basis of terminal half-life of the parent compound (2.62 h) and may be due in part to the active metabolite (UK-103,320).

40+ Years of HIV: Ramping up the Research

1994



The effect of zidovudine dose on the formation of intracellular phosphorylated metabolites

Michael G. Barry, Saye H. Khoo, Gareth J. Veal, Patrick G. Hoggard, Sara E. Gibbons, Edmund G.L. Wilkins*, Olwen Williams[†], Alasdair M. Breckenridge and David J. Back

AIDS 1996; 10: 1361-1367.

Intracellular PK

The first of 203 papers Saye & I published.

2000

Collaboration with Torino and C & W.



The unbound percentage of saquinavir and indinavir remains constant throughout the dosing interval in HIV positive subjects

Marta Boffito,^{1,2} Patrick G. Hoggard,¹ Helen E. Reynolds,¹ Stefano Bonora,² E Rhiannon Meaden,¹ Alessandro Sinicco,² Giovanni Di Perri² & David J. Back¹

¹Department of Pharmacology and Therapeutics, University of Liverpool, UK and ²Division of Infectious Disease, University of Torino, Italy

Br J Clin Pharmacol; 2002; 54: 262-268.

40+ Years of HIV: Ramping up the Research

2001



JOURNAL OF VIROLOGY, Nov. 2004, p. 12022–12029
0022-538X/04/\$08.00+0 DOI: 10.1128/JVI.78.21.12022-12029.2004
Copyright © 2004, American Society for Microbiology. All Rights Reserved.

Vol. 78, No. 21

Functional Correlation of P-Glycoprotein Expression and Genotype with Expression of the Human Immunodeficiency Virus Type 1 Coreceptor CXCR4

Andrew Owen,^{1*†} Becky Chandler,^{1†} Patrick G. Bray,² Stephen A. Ward,²
C. Anthony Hart,³ David J. Back,¹ and Saye H. Khoo¹

Pharmacogenetics

Repurposing of
anti-infectives!
*Antiviral activity
and synergy.*

In Vitro Synergy and Enhanced Murine Brain Penetration of Saquinavir Coadministered with Mefloquine

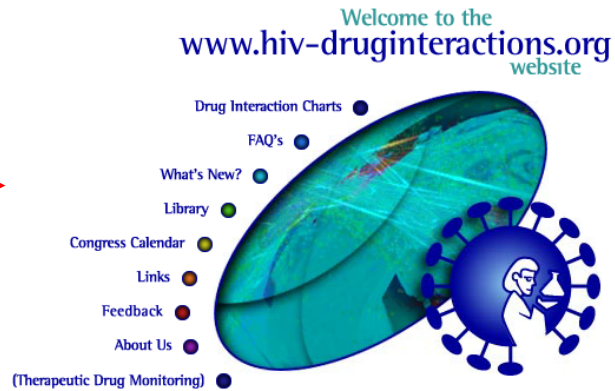
Andrew Owen, Omar Janneh, Ruben C. Hartkoorn, Becky Chandler, Patrick G. Bray, Phillip Martin, Stephen A. Ward, C. Anthony Hart, Saye H. Khoo, and David J. Back

Departments of Pharmacology and Therapeutics (A.O., O.J., R.C.H., B.C., P.M., S.H.K., D.J.B.) and Medical Microbiology (C.A.H.), The University of Liverpool, Liverpool, United Kingdom; and Liverpool School of Tropical Medicine, Liverpool, United Kingdom (P.G.B., S.A.W.)

40+ Years of HIV: Drug-Drug Interactions



1998: HIV Charts



1999: Web site

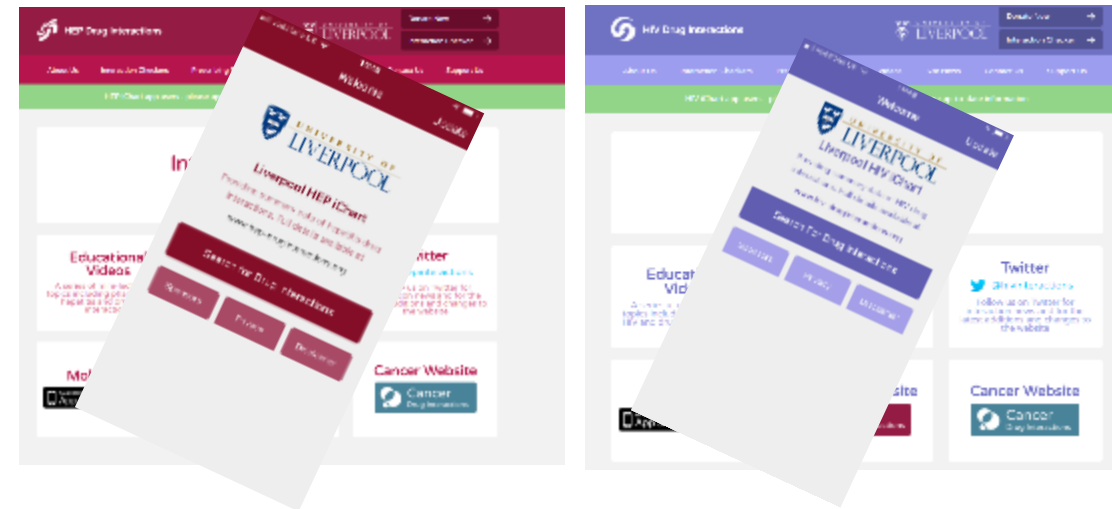


2006: Interactive Website

Saye Khoo
Sara Gibbons
Catia Marzolini
Fiona Marra
Alison Boyle
Justin Chiong
Katie McAllister
Jasmine Martin
Darryl Hodge
Daniel Seddon
Lauren Walker

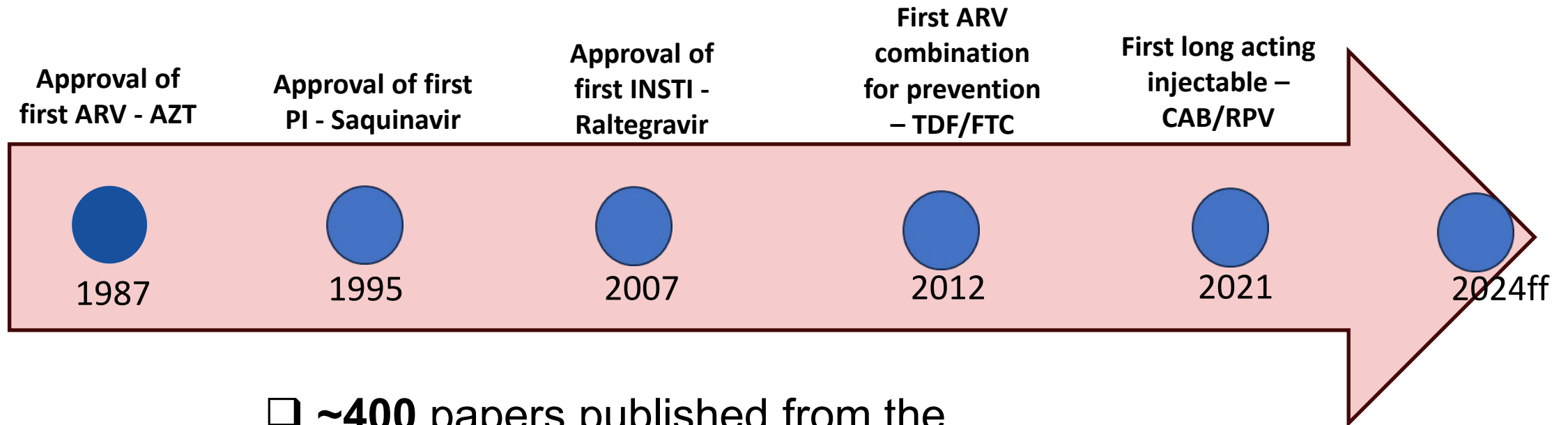


2020: Covid-19 website and App



2011: Redeveloped HIV site and App & launch of Hepatitis website and App (iOS, Android)

40+ Years of HIV: The Drugs



- ~**400** papers published from the department on ART and other antivirals

REVIEW

Toward Consensus on Correct Interpretation of Protein Binding in Plasma and Other Biological Matrices for COVID-19 Therapeutic Development

Marta Boffito^{1,2}, David J. Back³, Charles Flexner⁴, Peter Sjö⁵, Terrence F. Blaschke⁶, Peter W. Horby⁷, Dario Cattaneo⁸, Edward P. Acosta⁹, Peter Anderson¹⁰ and Andrew Owen^{3,11,*}

REVIEW

Recommendations for the Management of Drug–Drug Interactions Between the COVID-19 Antiviral Nirmatrelvir/Ritonavir (Paxlovid) and Comedications

Catia Marzolini^{1,2,*}, Daniel R. Kuritzkes³, Fiona Marra^{2,4}, Alison Boyle^{2,4}, Sara Gibbons², Charles Flexner⁵, Anton Pozniak^{6,7}, Marta Boffito⁶, Laura Waters⁸, David Burger^{9,10}, David J. Back² and Saye Khoo²

1

The PAST

2

The PRESENT

Pharmacology & Therapeutics

Centre of Excellence in
Long-Acting Therapeutics
(CELT)
Andrew Owen

Centre for Drug Safety
Science (CDSS)
Munir Pirmohamed



The Department
is widely
recognised as a
leader in HIV
pharmacology and
the quality, range
and innovation of
its research.

Centre for Experimental
Therapeutics (TherEx)
Saye Khoo

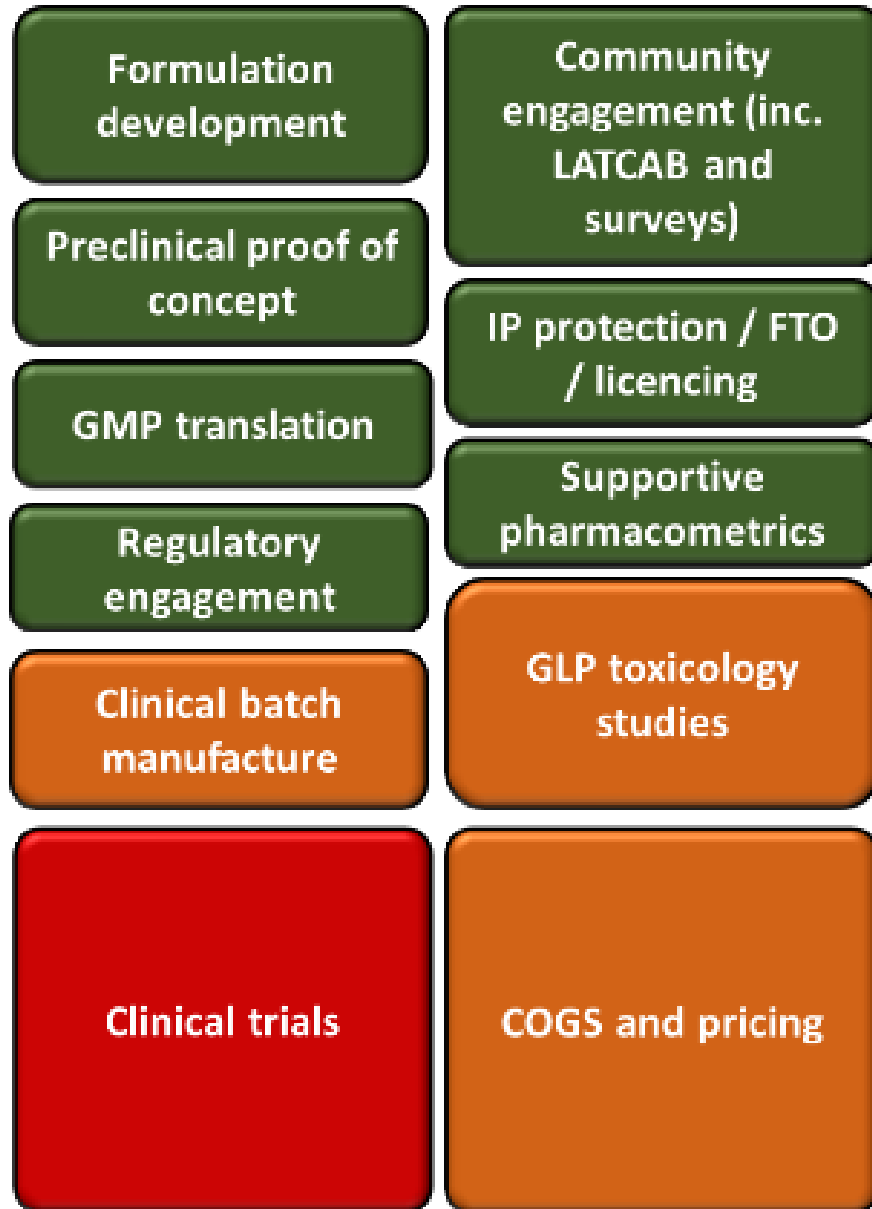
NIHR Clinical Research
Facility
Richard Fitzgerald

The Present: Centre of Excellence in Long-acting Therapeutics (CELT)



- First research centre of its kind in the world
- £40 million ongoing research funding
- 50 staff members in the centre.
- ~130 publications.

The Present: Ongoing activities of CELT Global Health



Preclinical Pharmacokinetics of Novel Long-Acting Tenofovir Alafenamide/Bictegravir Solid Injectable in Rats

Usman Arshad
University Of Liverpool.

Today 14.20

Dose Linearity Studies of a Glecaprevir and Pibrentasvir Long-Acting Injectable Formulation in Sprague Dawley Rats

Eduardo Gallardo-Toledo
University Of Liverpool.

Today 14.30

Perinatal and Paediatric Considerations for LA Medicines

Adeniyi Olagunju
University of Liverpool.

Today 15.45

Bioanalytical Facility (*Laura Else*)



- Early-phase trials of new drugs
- HIV, tuberculosis and Pandemic Therapeutics
- Medicines Optimisation, and Drug-Drug Interactions

PK Modelling Support (*Laura Dickinson*)



DynAIRx: Artificial Intelligence (AI)

Utilising advanced AI to support medicines optimisation in multimorbidity



 DynAIRx

Collaboration bringing together multiple stakeholders

Learning From Digital Records / AI Technology - The Need for Real Data

Lauren Walker – 19th at 4.15.



ASCPT Award – March 2024
Dolores Shockley Diversity and
Inclusion in Clinical Research
Award Lecture.

RESEARCH ARTICLE

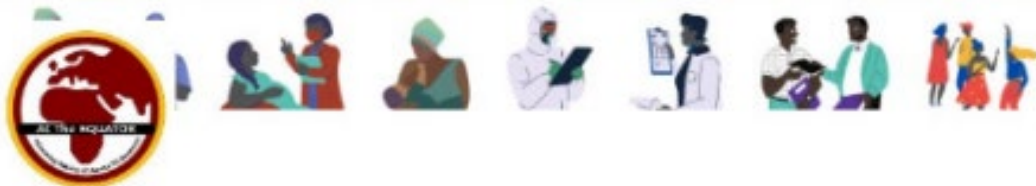
Safety and pharmacokinetics of dolutegravir in pregnant mothers with HIV infection and their neonates: A randomised trial (DOLPHIN-1 study)

Catriona Waitt^{1,2,3}, Catherine Orrell⁴, Stephen Walimbwa², Yashna Singh⁴, Kenneth Kintu², Bryony Simmons⁵, Julian Kaboggoza², Mary Sihlangu⁴, Julie-Anne Coombs⁴, Thoko Malaba⁶, Josephat Byamugisha⁷, Alieu Amara¹, Joshua Gini¹, Laura Else¹, Christie Heiburg⁴, Eva Maria Hodel³, Helen Reynolds³, Ushma Mehta⁸, Pauline Byakika-Kibwika², Andrew Hill¹, Landon Myer⁶, Mohammed Lamorde², Saye Khoo^{1,2,*}

Treating TB and HIV in neglected groups

The VirTUAL study is combining modelling and clinical research to identify the optimal drug treatments for pregnant women, children and adolescents with HIV and TB.

Attaining Equity of Access to Research (At The EQUATOR)



At The EQUATOR

Attaining Equity of Access To Research (At The EQUATOR)
Research Services · Kampala · 413 followers · 11-50 employees

Clinical Infectious Diseases

MAJOR ARTICLE

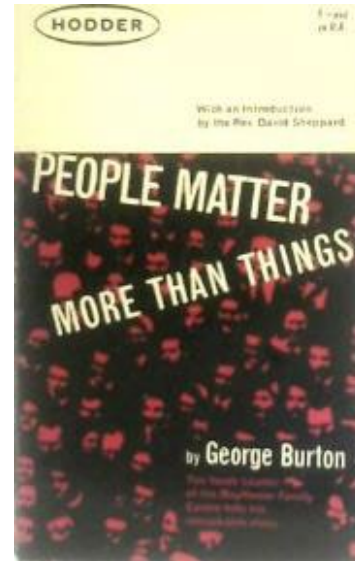


Pharmacokinetics and Safety of Twice-daily Ritonavir-boosted Atazanavir With Rifampicin

Kamukhwalwa Gausi,^{1,4,*} Henry Mugerwa,^{2,4} Marco Siccardi,³ Maiara Camotti Montanha,² Mohammed Lamorde,⁴ Lubbe Wiesner,^{1,6} Antonio D'Avolio,³ Helen McIlleron,⁷ Edmund Wilkins,⁶ Amedeo De Nicolò,^{5,6} Gary Maartens,^{1,4,6} Saye Khoo,¹ Cissy Kityo,¹ Paolo Dentì,^{1,6} and Catriona Waitt¹

¹Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa; ²Joint Clinical Research Centre, Research Department, Kampala, Uganda; ³Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, United Kingdom; ⁴Infectious Diseases Institute, Makerere University College of Health Sciences, Kampala, Uganda; ⁵Laboratory of Clinical Pharmacology and Pharmacogenetics, Department of Medical Sciences, University of Turin, Turin, Italy; and ⁶North Manchester General Hospital, HIV Research Unit, Manchester, United Kingdom

Do you want to know a secret?



The importance of:
Family
Friends
Faith

Case Report: 76 y Male

Amiodarone
Atorvastatin
Bisoprolol
Dapagliflozin
Edoxaban
Eplerenone
Losartan
Tamsulosin

People matter more than things!



Michael Barry



Ceppie Merry



Saye Khoo



Andrew Owen



Marta Boffito



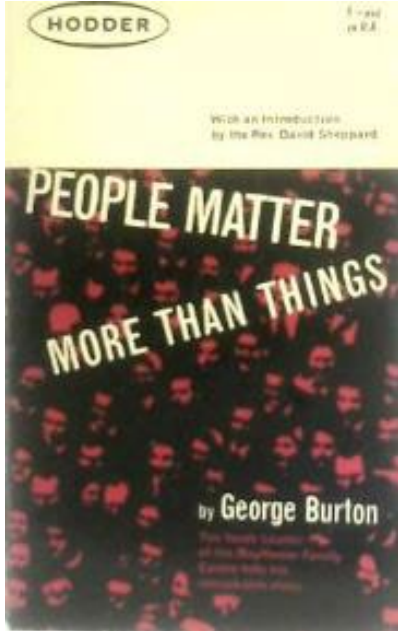
Catriona Waitt



Catia Marzolini



Richard Fitzgerald



Gerry Davies

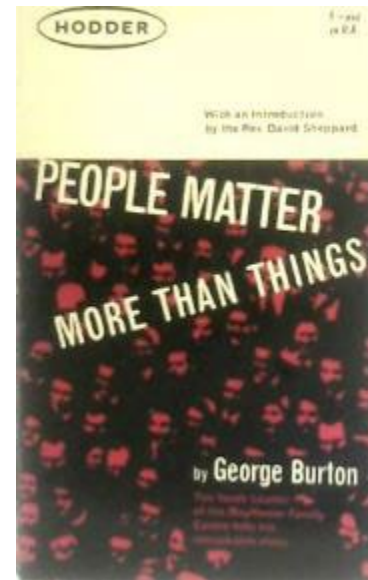


Gareth Veal



Neil Liptrott

People matter more than things!



25 Years of Great Meetings



2009 Amsterdam

25 Years of Great Meetings



2014, Washington DC



2019 Noordwijk (Followed by 2 years of Virtual)

Grateful Thanks

