Institution: University of Liverpool		
Unit of Assessment: UOA1 - Clinical Medicine		
Title of case study: Improving the clinical management of HIV and Hepatic Diseases worldwide: open access digital prescribing tools to optimise the management of drug-drug interactions		
Period when the underpinning research was undertaken: 2000 – November 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): **Prof. Saye Khoo** **Prof (Em). David Back**	**Role(s) (e.g. job title):** • Professor of Clinical Pharmacology and Honorary Consultant Physician • Professor of Pharmacology	**Period(s) employed by submitting HEI:** • 1998 – Present • • • 1973 – Present
Period when the claimed impact occurred: August 2013 – November 2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact (indicative maximum 100 words)

Drug-drug interactions (DDIs) are a major cause of harm, affecting 25% of people on HIV treatment. We developed prescribing tools to identify and manage DDIs in HIV and hepatitis. Our resources are now standard of care in over 30 countries, and have been translated into Spanish, Portuguese and Japanese. Between January 2017 and December 2019, over 17,500,000 interactions have been returned from 50,000 unique monthly users across 220 countries and territories. The tools identify missed DDIs in up to 95% of prescriptions and change clinical management in 55% of cases resulting in demonstrable economic benefit.

2. Underpinning research (indicative maximum 500 words)

We recognized the huge danger of drug-drug interactions (DDIs) with HIV and hepatitis treatments and were the first to report harmful DDIs involving HIV-TB coinfection [3.1]. We were also the first to report the beneficial boosting of HIV protease inhibitors in patients.

Between 2012 and 2018, we participated in large-scale studies to characterise the frequency and severity of DDIs worldwide. Of approximately 39,000 patients from the UK, Switzerland, Spain and Uganda, significant DDIs were reported in 18-35% of patients taking antiretrovirals [3.2-3.5]. DDIs with the highest risk and greatest consequence involved: antibiotics, antifungals, central nervous system drugs, cardiovascular drugs and corticosteroids.

With our expertise in DDIs, we developed an electronic point-of-care HIV drug interaction tool in 2000, providing prescribing support in the form of interaction recommendations on the likelihood of DDIs between HIV drugs and commonly prescribed co-medications. This involved the collation of all available drug information including University of Liverpool and external DDI studies, published drug labels and expert predictive pharmacokinetics. We also developed systematic evidence evaluations based on the GRADE method, where all interactions were given a score based on the quality of evidence [3.6].

In 2011, direct-acting antivirals (DAAs) were introduced to treat hepatitis C virus (HCV). Despite DAAs improving tolerability and efficacy, DDIs were an emerging challenge with the potential to cause patient harm and treatment failure. We recognised the clinical need for prescribing support and developed the hepatitis drug interaction tools. We have since expanded the hepatitis resources to include more hepatic diseases, including non-alcoholic steatohepatitis and hepatocellular carcinoma (2019).

Our DDIs tools are unique and work to current standards. Each tool has a disease-specific focus, working to our clinical and scientific expertise, allowing us to possess greater coverage than other DDI resources. We have systematically evaluated over 80,000 DDIs across all tools, providing detailed DDI commentaries for each interaction, whereas drug labels, in comparison, can often be particularly sparse. Our comprehensive database includes a wide range of co-medications including recreational drugs and herbal therapies. Our robust and transparent evidence evaluation process, developed over 20 years, ensures we always provide accurate and reliable drug information. We also include clinical management advice in our interaction recommendations

where possible. Quality assurance and ongoing maintenance is constantly undertaken, updating our tools in light of emerging data and guaranteeing our tools are consistently up to date.

3. References to the research (indicative maximum of six references)

1. Lamorde M, Byakika-Kibwika P, Okaba-Kayom V, Ryan M, Coakley P, Boffito M, Namakula R, Kalemeera F, Colebunders R, **Back D**, **Khoo S**, Merry C. Nevirapine pharmacokinetics when initiated at 200 mg or 400 mg daily in HIV-1 and tuberculosis co-infected Ugandan adults on rifampicin. *J Antimicrob Chemother* 2011 Jan;66(1):180-3. doi: 10.1093/jac/dkq411
2. Okoli C, Schwenk A, Radford M, Myland M, Taylor S, Darley A, Barnes J, Fox A, Grimson F, Reeves I, Munshi S, Croucher A, Boxall N, Benn P, Paice A, Wyk J van, **Khoo S**. Polypharmacy and potential drug–drug interactions for people with HIV in the UK from the Climate-HIV database. *HIV Medicine* 15 July 2020. doi:10.1111/hiv.12879
3. Deutschmann E, Bucher H, Jaeckel S, Gibbons S, McAllister K, Scherrer A, Braun D, Cavassini M, Hachfeld A, Calmy A, Battegay M, Cipriani M, Elzi L, Young J, López-Centeno B, Berenguer J, **Khoo S**, Moffa G, Marzolini C, Swiss HIV Cohort Study. Prevalence of potential drug-drug interactions in patients of the Swiss HIV Cohort Study in the era of HIV integrase inhibitors. *Clinical Infectious Diseases* July 2020. https://doi.org/10.1093/cid/ciaa918
4. López-Centeno B, Badenes-Olmedo C, Mataix-Sanjuan A, McAllister K, Bellón J, Gibbons S, Balsalobre P, Pérez-Latorre L, Benedí J, Marzolini C, Aranguren-Oyarzábal A, **Khoo S**, Calvo-Alcántara M, Berenguer J. Polypharmacy and Drug–Drug Interactions in People Living With Human Immunodeficiency Virus in the Region of Madrid, Spain: A Population-Based Study. *Clinical Infectious Diseases* July 2020 71(2) p353–362 https://doi.org/10.1093/cid/ciz811
5. Seden K, Merry C, Hewson R, Siccardi M, Lamorde M, Byakika-Kibwika P, Laker E, Parkes-Ratanshi R, **Back D**, **Khoo S**. Prevalence and type of drug–drug interactions involving ART in patients attending a specialist HIV outpatient clinic in Kampala, Uganda. *Journal of Antimicrobial Chemotherapy* Dec 2015 70(12) p3317-3322. doi: 10.1093/jac/dkv259
6. Seden K, Gibbons S, Marzolini C, Schapiro J, Burger D, **Back D**, **Khoo S**. Development of an evidence evaluation and synthesis system for drug-drug interactions, and its application to a systematic review of HIV and malaria co-infection. *PLOS ONE* 2017 Mar 12(3): e0173509. https://doi.org/10.1371/journal.pone.0173509

4. Details of the impact (indicative maximum 750 words)

We have developed a suite of world-leading prescribing tools to identify and manage drug-drug interactions (DDIs) in HIV and hepatology.

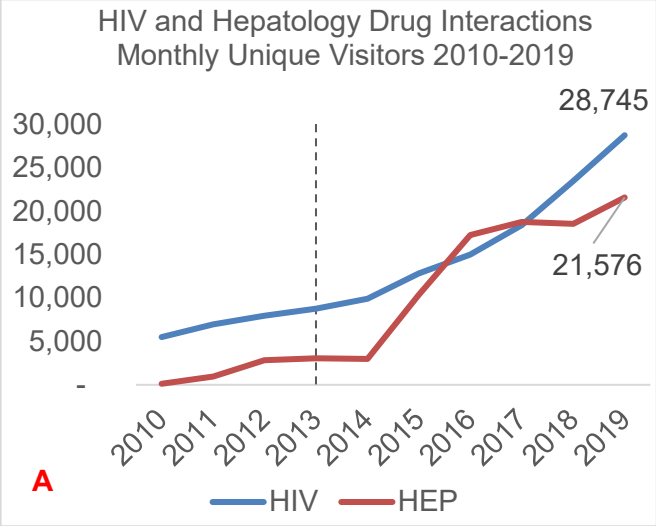
The DDI tools developed by Liverpool are available in many formats, allowing them to be accessible to as many healthcare professionals, researchers, and patients as possible. We have drug interaction websites, including low-bandwidth versions, and mobile apps for each disease area. We work with patient advocacy groups, such as i-Base, to determine the most appropriate and informative ways to provide drug information to patient audiences. Our DDI tools are used globally and have been integrated into electronic prescribing systems in Australia and Uganda. A Japanese version of our hepatology tool was launched in 2017 and Spanish and Portuguese versions of our HIV tool are launching in 2021. Building on the experience gained from developing HIV and hepatology prescribing tools, we identified a clinical need to expand our suite of tools to include cancer (2017) and COVID-19 (2020).

Our prescribing tools have delivered major impact in preventing harms as described below:

High uptake by prescribers worldwide and incorporation into national/international health policy

Since DDIs were identified as a challenge to the successful and cost-effective treatment of HIV and hepatic diseases, our DDI tools have been used by healthcare professionals in their clinical practice to optimise treatment and improve DDI management.

The tools have increased in importance as evidenced via the scale and geographical spread of their use [5.1]. Amount and breadth of usage of both the HIV and hepatology resources has consistently increased year-on-year since launch. As depicted below (figure A), the HIV and hepatology tools have over 50,000 users each month, from 220 countries and territories, responding to over 500,000 DDI queries [5.1]. The Liverpool tools are recommended for use in every HIV clinic in the UK [5.2], have established users across Western Europe and North America, and are increasingly used in Latin America, Asia and Africa [5.1].



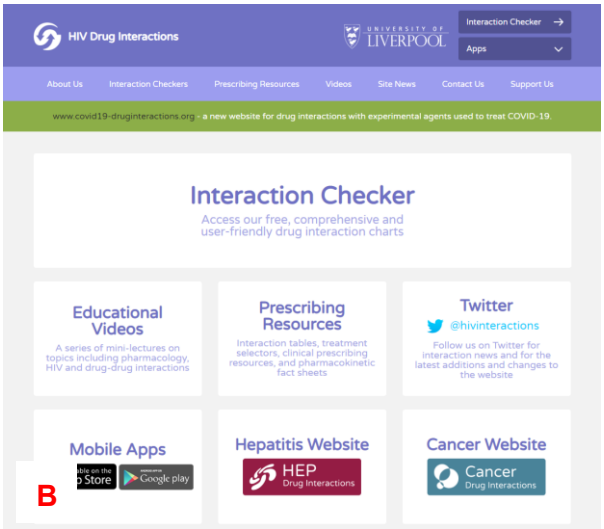


Figure A) Monthly average of unique users accessing the HIV and hepatology websites between 1st January 2010 and December 31st 2019. Figure B) Screenshot of HIV Drug Interactions website, which along with the HIV iChart app, make up the 'HIV tools'.

With established global use and continuous dissemination, the resources are recognised by national and international clinical associations and societies, and have been cited over 50 times in treatment guidelines in more than 20 countries [5.3]. Our DDI charts also form the basis of the DDI sections of the World Health Organization (WHO) HIV treatment guidelines, European HIV treatment guidelines and the European Association for the study of the Liver treatment guidelines [5.3]. With considerable global reach and influence, these treatment guidelines recognise our resources to be world leading DDI management tools.

The HIV tools (figure B) are recognised as being some of the most clinical useful and important resources in HIV clinical management, with the Chair of the WHO HIV Guideline Review Committee stating that "*WHO recognises the Liverpool HIV Drug Interactions website to be a world-leading resource….We rely on the information provided to develop global guidelines for the treatment and care of people living with HIV, and are very grateful to be able to reproduce the information from this site in our guidelines*" [5.4]. This is reinforced by the Chair of the British HIV Association, who said "*the Liverpool resources are cited as one of the most useful tools in HIV patient care. They are widely trusted and relied upon the world over. It is a great British invention, bringing benefit to patients and indispensable for prescribers*" [5.4].

The hepatology tools, developed almost 10 years ago, are also recognised as vital resources for clinical management of hepatic diseases. The President of the British Association for the Study of the Liver said that "*All those involved in HCV treatment would be lost without these trusted, freely available and up-to-date resources: they are a vital aspect of HCV patient care in the UK*" [5.4].This is supported by the Guidelines Chair of the European Association for the Study of the Liver, who said *"The efforts made by the authors had, and still have, a major influence on HCV treatment practices worldwide, in the context of eliminating viral hepatis as a public health threat by 2030*" [5.4].

Prevention of harm though demonstrable change in patient management as a direct result of actionable information

Between January 2017 and December 2019, over 17,500,000 DDIs have been queried using the HIV and hepatology tools. Approximately 23% of these queries have identified a potentially clinically significant DDI. Knowledge of an interaction can avoid harm to the patient and thereby reduce healthcare costs [5.1].

One specific example of how the DDI tools have prevented harm to patients is the integration of the HIV drug interactions checker into the electronic prescribing systems of one of the largest HIV clinics in sub-Saharan Africa (the Infectious Diseases Institute, Uganda). Since 2013, internal data and patient surveys have indicated that this integration has reduced the prevalence of significant DDIs in 4,556 patients by one third, with half of all affected prescriptions being subsequently altered. A follow up study used the HIV checker to carry out DDI screening in clinics where the tool had not been integrated. At baseline study visits, prescribers were aware of only 4.60% of clinically significant DDIs. Performing DDIs checks with the tools provided new information in 60.20% of cases and directly changed patient management in 55.60% of cases [5.5].

Changes in clinical practice and knowledge transfer

By identifying and addressing knowledge gaps in both drug interaction studies and DDI education, we have contributed to changes in drug labelling and clinical behaviour, resulting in changes to clinical practice.

In 2013, for example, we investigated the pharmacokinetics of artemether, dihydroartemisin (DHA) and lumefantrine during and after stopping rifampicin. Administration of rifampicin and artemether-lumefantrine significantly decreased levels of artemether (89%), DHA (85%) and lumefantrine (68%) compared to artmether-lumefantrine alone [5.6]. Prior to the study, no data existed on these drug interactions, but drug labels have since been revised to state that concomitant use of artemether-lumefantrine with rifampicin is contraindicated [5.6-5.7].

In addition to the need for prescribing support tools, we have also recognised the need for improved DDI education. We have developed and hosted educational events, demonstrating the utility of the tools to aid clinical management. These events have taken different forms: we have hosted symposia sessions at HIV Glasgow and the European AIDS Conference (EACS), collaborated with Virology Education to deliver events in Europe and have now developed virtual educational events for a global audience in 2020. Our events have been very popular, with recent sessions at EACS 2019 and IAS 2019 having 700 – 1,000 attendees.

With each event, the content is adapted to focus on emerging topics in HIV and hepatology clinical management whilst also being tailored to meet the educational requirements of a particular audience, context or setting. We work with our global network of key opinion leaders, supporters and advocates to ensure the content of each event is of the highest standard and clinical relevance.

In November 2020, we developed and hosted an online educational event, 'Liverpool Masterclass in Antiviral Pharmacology'. The workshop was targeted at healthcare professionals with a focus on the Liverpool tools and clinical pharmacology of DDIs in HIV, hepatology, cancer and COVID-19. A series of interactive and engaging talks and cases were given by Liverpool faculty and members of the drug interaction group. We also encouraged registrants to submit cases to be discussed during the workshop.

Accredited by the Royal College of Physicians, the workshop had 281 attendees from 35 countries. Workshop feedback was extremely positive, where 100% of survey participants would recommend the meeting to a colleague, 97% of participants (strongly) agreed that the workshop was relevant to their clinical practice and 94% of participants (strongly) agreed that they had a better understanding of the role of the Liverpool tools in patient management [5.8].

Economic benefits to healthcare systems

Between January 2017 and December 2019, the HIV tools had an average of over 23,000 unique monthly users, from 220 countries and territories, searching for over 8,500,000 interactions, of which 2,000,000 were classified as clinically significant [5.1] and were either contraindicated combinations or required clinical intervention (monitoring and/or treatment change). Alerts for clinically significant DDIs have resulted in avoidance of harm to patients and potential cost savings to healthcare systems.

Using the Liverpool tools, Demessine et al. have estimated the cost of HIV-related DDIs to the French healthcare system to be approximately GBP2,021 for 1-year follow-up per individual (USD2,693 (03-2019)) [5.9].

Using data from the Climate-HIV database, 0.90% of HIV patients in the UK, of which there are estimated to be 100,000, are prescribed a medication which is contraindicated. Through the avoidance of such drug combinations, we estimate savings of approximately GBP1,818,900 [5.10].

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Analytics Report produced by the Liverpool Drug Interactions Group in 2020, detailing key metrics of tool usage and geographical spread between January 2017 – December 2019.
2. British HIV Association (BHIVA) guidelines for the treatment of HIV-1-positive adults with ART 2015 (2016 interim update). Recommends all UK HIV clinics to advise using the Liverpool HIV tools.
3. Clinical Treatment Guidelines and Policy documents, recommending and citing hiv-druginteractions.org and hep-druginteractions.org, produced by the Liverpool Drug Interactions Group in November 2020.
4. Letters from WHO Guideline Review Committee Chair, Chair of British HIV Association, and President of the British Association for the Study of the Liver confirming support of the Liverpool drug interactions tools.
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7. Prescribing information for Riamet (artemether/lumefantrine) tablets, using data from corroborating evidence 5.6 to inform clinical management.
8. Formal report and survey data from 'Liverpool Masterclass in Antiviral Pharmacology (LMAP)' -an educational workshop hosted in November 2020.
9. Demessine L, Peyro-Saint-Paul L, Gardner EM,Ghosn J, Parienti JJ. Risk and Cost Associated With Drug-Drug Interactions Among Aging HIV Patients Receiving Combined Antiretroviral Therapy in France. *Open Forum Infectious Diseases* March 2019; 6(3) doi: 10.1093/ofid/ofz051
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