

Glasgow notes

The following very rough notes cover some of the interesting studies in Glasgow. I've pasted some of the abstracts at the end, although abstract text is also fairly technical.

The main points included:

- Better treatment response to HCV treatment in people with coinfection
- The way children in the UK are treated in terms of taking longer to switch treatment
- Explanation of why a trial of new NNRTI called TMC-125 (etrivirine) was stopped early because of poor responses
- Overview of drug interactions for the new protease inhibitor TMC-114 (darunavir)
- Side effects for d4T in Malawi
- Discussion about kidney side effects and tenofovir – how to look at different reports

If we still have more time then the other things there included:

- Genetics and EFV - support higher drug levels in African pts
- Gemini study – comparing SQV/r vs LPV/r Interim analysis + higher failure in SQV vs LPV. Slightly better lipid profile favours SQV, but earliest data using old formulation of Kaletra.
- TDM for EFV in coinfecting people with cirrhosis
- TPV/r vs DRV/r in people with extensive PI resistance – what is the difference between these 2 new drugs.

i) Hepatitis coinfection

HCV: overview by Jurgen Rockstroh - higher HCV SVR rates with higher RBV dose 1000-1200mg in PRESCO trial in both Genotype1/4 and 2/3 and that longer treatment (72wks/48wks) approaches result rates in mono-infection with shorter treatment. Also, telaprevir (in HCV coinfection, -8 log drop in 4 weeks with IFN+RBV, interactions with HIV PIs?); and telbivudine for HBV (-7 log in mono-infection)

PL/13.1

In an intent-to-treat analysis, sustained virological response (SVR) was achieved by 49.6%, significantly higher in 152 HCV-2/3 than 237 HCV-1/4 patients (72.4% vs 35%; p<0.0001). Furthermore, the SVR was higher in patients allocated to extended versus shorten treatment arms (53% vs 31% for HCV-1/4 and 82% vs 67% for HCV-2/3), although a high drop-out rate in the former precluded to obtain definitive conclusions. Premature treatment discontinuations due to serious adverse events occurred in 8.5% of patients. [+earlier data in P314]

ii) Children in UK

In the UK a large group of children are treated very differently to the established approach for adult care - ie very late switching. Another UK study reported 2/6 deaths this year were related to MDR HIV and no treatment options. TMC-114 was included as a successful case report and paediatric formulations raised by Di Gibb in separate presentation.

PL 2.4 - 132 (22%) of 595 children (median age 4.7 years) initiating HAART naïve switched to 2nd-line therapy after a median 7 years (rate 7.8/100 child-yrs (CY) [95%CI 6.6-9.2]). Median (IQR) CD4 count (%) at switch was 485 (217-840) cells/mm³ (20% (12-26)) but only 63 (48%) had achieved VL <400 during 1st-line. VL at switch was 8206c/ml (5382-12512) in children who had suppressed vs 79569c/ml (62127-101907) in those who had not; time to switch was also longer (median >7 vs 3.1 yrs respectively, adj HR=0.12 [0.08-0.19]).

+ P360 – six children with MDR this year (2 died)

Median number of drugs ever received 13 (range 9-14) and 3 had T20. At latest follow up all have detectable VL (range 121 to >500,000 c/ml) half have a CD4 count of 0 (range 0-410).

+ P371

EAP use of TMC-114 + T-20 in one MDR child leading to dramatic reduction in viral load (though still detectable at around 2000c/mL at report)

Issue of paediatric formulations highlighted in separate presentation form Di Gibb

iii) Explanation for TMC-125 227 study failure

This is important as study was closed by Data and Safety Monitoring Board (DSMB) because one group significantly failed to show minimum virological response. 227 was a study of a new NNRTI in people who were failing their first-line NNRTI-based regimen and who were PI-naïve. Randomisation was to the new NNRTI or PI. extensive RTI and NNRTI resistance, and recycling of RTIs. Showed that accumulating NNRTI mutation can compromise chance of benefiting from pipeline NNRTIs.

At baseline, median number of NNRTI mutations was 2 (range 0-4) and median fold change (FC) to TMC125 was 2.0. Median number of NRTI mutations was 1 (range 0-7), 9% and 12% of subjects in TMC125 and control groups, respectively, did not receive two sensitive NRTIs. Patients with higher TMC125 FC also frequently had higher numbers of NNRTI and NRTI mutations.

iv) Drug interactions with TMC-114 and TMC-125

Two presentations presented interaction data with TMC-114 (main ARV contraindication is with SQV and LPV though explanation of the interactions not clear) and 125 (can be used with DRV)

v) Side effects from d4T-based treatment

PN in Malawi (however measured – ie ~10% on amitriptyline, some switch to AZT, but 35% with symptoms that could be PN); and diabetes mellitus in D:A:D study (2-3 year exposure – 8-fold higher risk).

WHO recommendations 'so that some governments may want to choose alternative options' ignore reality of cost. Depressing to hear that Malawi has ordered d4T-based for at least next year.

1. Discussion issue on renal complications and TDF:

Renal disease ~ 12 posters – as with many conferences in LB presentation (13.2) from EAP programme:

5% (62/826) developed Cr ≥ 1.3 x BL and 20% (236/1182) discontinued TDF, including 66 (6%) who died. In multivariate analysis, factors associated with Cr ≥ 1.3 x BL were concomitant ddi (OR 2.14; p=0.015), BL CD4 (OR 1.59/ 100 cell decrement; p<0.0001), and female gender (OR 2.33; p=0.029).

~25% renal dysfunction at baseline in some reports (P147). Other studies show up to 38% changes in GFR after 1 year on TDF (P148).

Most show only changes associated with mild renal dysfunction in terms of reduced GFR and few if any renal discontinuations.

ie:

P152 – 903 study: 86 patients on TDF/FTC/EFV with 5-year f/u, no renal d/c, 2 grade 1 serum Cr >1.5; no fanconi, stable Cockcroft-Gault

P6 – 96 week TDF/FTC vs AZT/3TC

But both only show median range with IQR rather than full range of changes, and compare baseline to endpoint changes for statistical significance rather than comparison for trend between different treatment arms.

P154 – SCOLTA – 9/354 (2.5%) – most IDV and HCV coinfecting with renal dysfunction at baseline

P155 – Edinburgh study – n=78 on >12mo TDF; protective effect in African pts

P156 – St Georges – n=69 TDF vs 90 non-TDF; no sig differences in CrCl but African pts less likely to improve CrCl if on TDF.

P157 – renal safety in naïve pts with mild renal impairment, hypertension or DM +/- TDF: no significant difference vs thymidine analogue

P153 – similar rates of mild renal changes in TDF (25%) vs non-TDF (23%) regimens

P149 – UCL study – 1.4% renal toxicity (20/1406 pts on TDF); 17/20 normal CrCl at baseline, 19/20 increased proteinuria on TDF.

5 others:

vi) STI with detectable viral load UK-CHIC – STI when viral load >50 copies/mL is associated with increased risk of future viral rebound. No link when <50 copies/mL at STI. These results are the opposite of the published abstract.

vii) Genetics and EFV - support higher drug levels in African pts

viii) Gemini – SQV/r vs LPV/r Interim analysis + higher failure in SQV vs LPV. Slightly better lipid profile favours SQV, but earliest data using old formulation of Kaletra.

ix) TDM for EFV in coinfecting people with cirrhosis

x) TPV/r vs DRV/r Greater patient numbers with TPV, also higher RTV dose and concern from liver toxicity.

[PL13.1] The PRESCO trial: role of extended duration of therapy with pegylated interferon alfa-2a plus weight-based ribavirin dose in 389 HCV/HIV co-infected patients *Marina Nuñez, Celia Miralles, Miguel A Berdún et al on behalf of the PRESCO Study Group.*

Purpose of the Study The treatment of chronic hepatitis C has become a priority in HIV+ patients. The poorer therapeutic response in coinfecting patients compared to HCV-monoinfected individuals could be due to the use of low flat (800 mg/day) ribavirin (RBV) doses and/or short lengths of therapy in prior trials. *Methods* In a prospective, multicenter, open, comparative trial, coinfecting patients with CD4 >300 cells/μl and elevated aminotransferases who had not previously been exposed to interferon received pegylated interferon alfa-2a (180 μg per week) plus RBV (1000 mg daily if body weight <75 Kg; 1200 mg daily if >75 kg). Patients with HCV genotypes 1 and 4 were treated for 48 or 72 weeks, while patients with HCV genotypes 2 and 3 were treated for 24 or 48 weeks. *Summary of Results* Out of 389 patients included in the trial, 61% were infected by HCV-1/4 and 67% had serum HCV-RNA >500,000 IU/ml. In an intent-to-treat analysis, sustained virological response (SVR) was achieved by 49.6%, significantly higher in 152 HCV-2/3 than 237 HCV-1/4 patients (72.4% vs 35%; p<0.0001). Furthermore, the SVR was higher in patients allocated to extended versus shorten treatment arms (53% vs 31% for HCV-1/4 and 82% vs 67% for HCV-2/3), although a high drop-out rate in the former precluded to obtain definitive conclusions. Premature treatment discontinuations due to serious adverse events occurred in 8.5% of patients. Infection with HCV-2/3, lower baseline HCV-RNA, and HCV-RNA <50 IU/ml at week 12 were independent predictors of SVR in the multivariate analysis. *Conclusions* PRESCO is the largest trial conducted so far in coinfecting patients using pegIFN plus RBV. The use of 1000-1200 mg/day of RBV was relatively safe and provided SVR in nearly half of HCV/HIV-coinfecting patients, twice higher in HCV-2/3 than HCV-1/4 carriers. Both the use of higher RBV doses and extended duration of therapy most likely explained the better responses in this study compared to prior trials conducted in coinfecting patients.

[PL2.4] Wide disparity in switch to second-line therapy in HIV-infected children in CHIPS *K J Lee, H Lyall, A S Walker, M Sharland, A Judd, D M Gibb. CHIPS Steering Committee, London, UK*

Purpose of the Study To describe characteristics of switch to 2nd-line therapy in children initiating HAART naïve in the UK & Ireland Collaborative HIV Paediatric Study. *Methods* We examined CD4 and viral load (VL) at switch to 2nd-line, defined as substituting either ≥3 drugs in the regimen or 2 drugs with recorded reason failure, with VL >50 c/ml. We considered timing of switch with respect to various VL thresholds. *Summary of Results* 132 (22%) of 595 children (median age 4.7 years) initiating HAART naïve switched to 2nd-line therapy after a median 7 years (rate 7.8/100 child-yrs (CY) [95%CI 6.6-9.2]). Median (IQR) CD4 count (%) at switch was 485 (217-840) cells/mm³ (20% (12-26)) but only 63 (48%) had achieved VL <400 during 1st-line. VL at switch was 8206c/ml (5382-12512) in children who had suppressed vs 79569c/ml (62127-101907) in those who had not; time to switch was also longer (median >7 vs 3.1 yrs respectively, adj HR=0.12 [0.08-0.19]). Considering sex; age, CD4%, prior clinical (B,C) events and calendar year at HAART

initiation, and achieving VL<400 c/ml during 1st-line, only older age and later calendar year independently predicted earlier switch (adj HR=1.07 [1.02-1.13] per year older; HR=2.27 [1.24-4.16] starting HAART in 2002-05 compared to 1997-99). By 3 years after HAART, 14% & 18% switched before reaching VL thresholds of 1000 and 30000c/ml respectively (as in the PENPACT 1 trial); 3% & 1% reached thresholds and switched within 6 months with 15% & 3% remaining on 1st-line for at least 6 months after confirmed VL >1000 or >30000. Median time to switch after thresholds was 3.3 and 1.0 yr respectively. *Conclusions* CD4 and VL, and timing of switch in relation to different VL thresholds vary widely in children across all ages. There is urgent need for evidence on which to base switching.

[P360] Emerging multi-drug resistance in children with perinatally acquired HIV-1 *C Foster, N Mackie, P Seery, S Walters, G Tudor-Williams, H Lyall. Family Clinic, St Mary's Hospital, London, UK; GUM, St Mary's Hospital, London, UK; Family Clinic, Chelsea and Westminster Hospital, London, UK* *Purpose of the Study* Children with HIV are surviving into adolescence, but prolonged ARV exposure and non-suppressive regimens increase the risk of accumulating mutations associated with resistance to HIV-1. We evaluated the prevalence of triple class genotypic resistance (MDR HIV) and clinical outcome in a paediatric cohort. *Methods* Retrospective case note audit of children attending 2 Family HIV clinics 1/06-6/06. Demographic, ARV, CD4 count and VL data collected. Significant mutations defined along IAS guidelines. *Summary of Results* 236 HIV infected children median age 9.8yrs (range 0.4-17.7), 196 (83%) have ever received ARVs. 6/196 (3%) had MDR HIV on genotyping; half were male, five of black African origin, current median age 13.5yrs (range 5.3-17.6). Median time on ARVs 10.6yrs (range 3.9-14.2) but 5/6 children took dual therapy prior to HAART availability. Median number of drugs ever received 13 (range 9-14) and 3 had T20. At latest follow up all have detectable VL (range 121 to >500,000 c/ml) half have a CD4 count of 0 (range 0-410). All have multiple TAMS, 5/6 have M184V, and all have NNRTI resistance mutations, most commonly Y181C (4/6). Protease mutations occurred most frequently at position 46 (5/6), 82 (4/6) and 84 (3/6). One patient continues T20, TMC114/r and optimised background (OB), CD4 410, VL 2679 c/ml. A second recently commenced TMC114/r, TMC125 and OB; VL fell from 144,000 to 121 c/ml at day 14. A 5yr old girl on 3TC/DDI awaiting novel ARVs died of overwhelming sepsis during the study period. Of the 3 remaining children 2 continue failing PI regimens, the third 3TC monotherapy. *Conclusions* Perinatally infected children with MDR HIV living in the UK urgently require access to novel salvage therapies to survive.

[PL5.6] Impact of NNRTI and NRTI resistance on the response to the regimen of TMC125 plus two NRTIs in Study TMC125-C227 *B Woodfall, J Vingerhoets, M Peeters, I Peeters, G De Smedt, GD Miralles, M.P. de Béthune. Tibotec BVBA, Mechelen, Belgium* *Purpose of the Study* TMC125 is a novel NNRTI with antiviral activity against NNRTI-resistant HIV-1. TMC125-C227 was an exploratory Phase II trial comparing TMC125 and a PI, given with two NRTIs, in NNRTI-resistant but PI-naive patients after first-line NNRTI failure. *Methods* Patients with evidence of NNRTI resistance were randomized to TMC125 (N=59) or an investigator selected PI (N=57) with a backbone of 2 investigator-selected, sensitive NRTIs. Treatment with TMC125 was prematurely discontinued due to suboptimal virologic response compared to control. *Summary of Results* At baseline, median number of NNRTI mutations was 2 (range 0-4) and median fold change (FC) to TMC125 was 2.0. Median number of NRTI mutations was 1 (range 0-7), 9% and 12% of subjects in TMC125 and control groups, respectively, did not receive two sensitive NRTIs. Patients with higher TMC125 FC also frequently had higher numbers of NNRTI and NRTI mutations. For patients reaching week 12, 57% and 91% achieved at least 1 log₁₀ viral load decline in TMC125 and control groups, respectively. PK, baseline CD4 and viral load were not associated with virologic response. In contrast, increased numbers of NRTI and NNRTI mutations, use of inactive NRTIs, and higher TMC125 FC were associated with virologic failure. *Conclusions* In this study, in PI-naive patients having failed a first-line NNRTI regimen, the level of NNRTI and NRTI resistance was higher than expected. Since patients were PI naive, these higher levels of baseline resistance probably account for the difference in outcome between the TMC125 and PI arms. Given the demonstrated long-term virological benefit of TMC125 in patients with NNRTI and PI resistance, evaluation of TMC125 in NNRTI and PI experienced patients continues in ongoing Phase III trials.

[P145] Peripheral neuropathy in patients at the Lighthouse Clinic, Lilongwe, Malawi *Wendy I Beadles, Daniel Clutterbuck, Andreas Jahn, Ralf Weigel. Regional Infectious Diseases Unit, Western General Hospital, Edinburgh, UK; Department of Genitourinary Medicine, Edinburgh Royal Infirmary, Edinburgh, UK; Lighthouse Clinic, Kamuzu Central Hospital, Lilongwe,*

Malawi *Purpose of the Study* A retrospective analysis of the prevalence and management of peripheral neuropathy (PN) in a cohort of 3341 patients on HAART in a resource limited setting. Lighthouse uses Triomune (Stavudine (D4T)/ Lamivudine/ Nevirapine) as 1st line antiretroviral (ARV) regimen, for clinically eligible patients. D4T and HIV related PN are common, but diagnosis is difficult. Amitriptyline is widely prescribed in this setting for treatment of painful neuropathy. In cases of persistent or escalating symptoms, national guidelines recommend substitution of D4T by Zidovudine (AZT). *Methods* Cross sectional analysis of all ARV patients attending during quarter 1, 2006. The database was screened for patients with direct or indirect evidence for PN: 1. Reporting leg pain and/ or numbness (using routine checklist review). 2. Explicit diagnosis of PN. 3. Prescription for Amitriptyline. 4. Patients on AZT containing regimen. *Summary of Results* 3341 patients were prescribed ARV's of which 6% were on an AZT containing regimen. Leg pain and/or numbness were reported for 1173 (35%) patients on ARV's. However only 428 (13%) were given a diagnosis of PN and 228 (7%) were prescribed Amitriptyline. *Conclusions* Peripheral neuropathy is common in this setting and poses significant challenges in assessment. Screening with checklists may over estimate the true prevalence. 1/3 of patients are currently reporting symptoms suggestive of PN and approximately 10% receive symptomatic or alternative treatment. Validation of the clinical diagnosis of PN, grading systems and randomised trials of the use of Amitriptyline and early versus late switch of therapy are required.

[PL9.5] Relationship between use of stavudine and diabetes mellitus *S De Wit, CA Sabin, R Weber, SW Worm, P Reiss, R Thiebaut, W El-Sadr, A D'Arminio Monforte, E Fontas, MG Law, AN Phillips, N Friis-Moeller, JD Lundgren. St-Pierre Hospital, Brussels, Belgium; Royal Free Hospital, London, UK; Copenhagen HIV Program for the D:A:D Study Group, Copenhagen, Denmark* *Purpose of the Study* The incidence of diabetes mellitus (DM) in the D:A:D study is comparable to that in HIV-ve populations. This analysis aims to identify whether specific antiretrovirals (ARV) were associated with new onset DM. *Methods* D:A:D is a prospective observational study of 23,437 HIV patients (p); DM is collected as a study endpoint. Poisson regression models assessed the relation between DM and exposure to ARV after adjusting for risk factors for DM (age, sex, race, body mass index, smoking), CD4 count, lipodystrophy, calendar year and lipids. *Summary of Results* 435 p. developed DM over follow-up (rate 5.89/1000 person-years [PY]). The rate of DM (/1000 PY) increased from 3.96 in those unexposed to stavudine to 8.20 in those exposed for 2-3 years and then decreased. No other ARV was significantly associated with DM after controlling for stavudine use. The non-linear relationship with stavudine remained significant after adjusting for risk factors for DM. Time-updated total cholesterol (relative rate 1.06/mmol/L, p=0.07), HDL-cholesterol (0.47/mmol/L, p=0.0001) and triglycerides (6.35/doubling, p=0.0001) were all associated with DM. Adjusting for each of these separately reduced slightly the relationship between stavudine and DM. While lipodystrophy was significantly associated with DM (1.37, p=0.008), adjustment for this did not modify the relationship between stavudine and DM. *Conclusions* Stavudine is significantly associated with DM after adjustment for risk factors for DM and lipids. Adjustment for lipodystrophy did not modify the relationship, suggesting that stavudine potentially directly contributes to insulin resistance, rather than through lipodystrophy.

[PL5.1] Use of TMC114 in combination with other drugs: guidance from pharmacokinetic studies *D Back, V Sekar, E Lefebvre, M De Pauw, E De Paepe, T Vangeneugden, R Hoetelmans. University of Liverpool, Liverpool, UK; Tibotec Inc., Yardley, USA; Tibotec BVBA, Mechelen, Belgium* *Purpose of the Study* Drug interactions (DIs) are a practical concern when treating HIV-infected patients. Pharmacokinetic (PK) interactions between TMC114 with low-dose ritonavir (TMC114/r) and other drugs used in HIV-infected patients are presented. *Methods* Clinical studies were conducted to assess effects of combining TMC114/r with other drugs based on in-vitro findings and theoretical considerations for potential PK interactions. TMC114/r was studied with atazanavir (ATV), indinavir (IDV), lopinavir/r (LPV/r), saquinavir/r (SQV/r), efavirenz (EFV), nevirapine (NVP), tenofovir disoproxil fumarate (TDF), atorvastatin (AVS), omeprazole (OME), ranitidine (RAN), sildenafil (SIL), clarithromycin (CLA), sertraline (SER), paroxetine (PAR), oral contraceptives (OC) and ketoconazole (KTZ). *Summary of Results* TMC114/r increased exposure to EFV (21%), NVP (27%), TDF (22%), IDV (23%), LPV (37%), KTZ (212%), CLA (57%), AVS and SIL (4-fold), and decreased exposure to SER (49%), PAR (39%) and ethinyl estradiol (44%). There was no change in ATV or SQV. TMC114 exposure increased by 21%, 24% and 42%, respectively, when combined with TDF, IDV and KTZ, decreased by 13%, 13%, 26% and 53%, respectively, when combined with EFV, CLA, SQV/r and LPV/r, and was unchanged when

combined with ATV, NVP, AVS, OME, RAN, SER and PAR. *Conclusions* TMC114/r can be combined with many drugs with no TMC114/r dose adjustments. Some co-administered drugs may require dose adjustments (SIL, AVS, KTZ and IDV). Combining TMC114/r with LPV/r or SQV/r is not recommended. Additional contraception should be used when OC are combined with TMC114/r. Current evidence shows that DIs between TMC114/r and drugs commonly used in HIV-infected patients are well characterised and manageable.

Summary of Results

TMC114/r increased exposure to

Efavirenz (+21%)

Nevirapine (+27%)

Tenofovir (+22%)

Indinavir (+23%)

Lopinavir/r (+37%)

Ketoconazole (+212%)

Clarithromycin (+57%)

Atorvastatin (+400%) and

Sildenafil (+400%)

TMC114/r decreased exposure to

sertraline (-49%)

paroxetine (-39%) and

ethinyl estradiol (-44%).

There was no change in ATV or SQV.

TMC114 exposure increased by:

TMC114 (+21%) with TDF

TMC114 (+24%) with IDV

TMC114 (+42%) with KTZ

TMC114 exposure decreased by:

TMC114 (-13%) with EFV

TMC114 (-13%) with CLA

TMC114 (-26%) with SQV/r

TMC114 (-53%) with LPV/r

TMC-114 was unchanged when combined with ATV, NVP, AVS, OME, RAN, SER and PAR.

[PL13.2] Predictors of creatinine (Cr) increase and drug discontinuation in patients receiving tenofovir DF (TDF) *M Harris, R Joy, N Zalunardo, R Werb, B Yip, R Hogg, J Montaner. AIDS Research Program, St. Paul's Hospital, Vancouver, BC, Canada; BC Centre for Excellence in HIV/AIDS, Vancouver, BC, Canada; Division of Nephrology, University of BC, Vancouver, BC, Canada*

Purpose of the Study TDF use in the EAP was associated with clinically significant Cr increases, seen earlier in patients with lower CD4. Since approval, TDF use is not restricted by previous ARV, CD4, renal function or concomitant medications. We examined factors associated with Cr increase and TDF discontinuations (d/c) using a database including ARV history and lab values. *Methods* HIV+ adults starting TDF 01/01/03 to 31/05/05 and with ≥ 1 Cr within 6 mo of TDF start and ≥ 1 Cr while still on TDF were included. Endpoints were Cr ≥ 1.3 x pre-TDF baseline (BL) or TDF d/c for any reason. Logistic regression was used to calculate unadjusted and adjusted odds ratios (OR). Event-free subjects were right censored at the last Cr test up to 31/10/05.

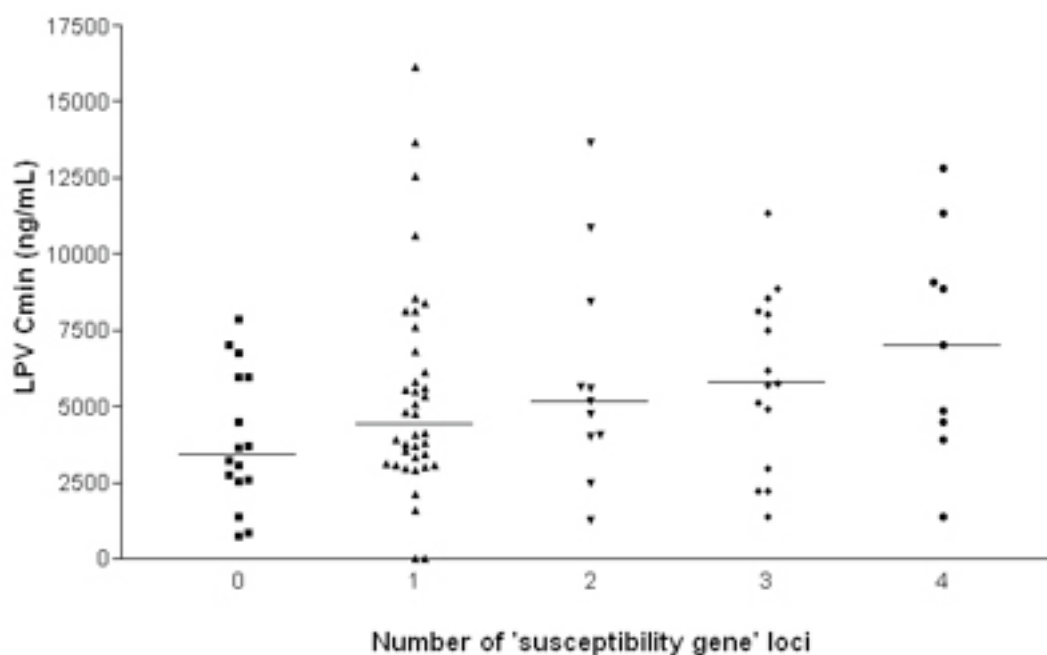
Summary of Results Analysis includes 1182 patients: 1000 male (85%), 188 ARV naïve (16%), 265 with AIDS (22%), median age 42 yrs, previous ARV 34 mo, CD4 220/mm³, VL 24,500 c/mL, Cr 83 μ mol/L, GFR 92 mL/min/1.73m². Concomitant ARV included ddl in 406 (34%) and boosted PIs in 967 (82%). Median time on TDF was 12.2 mo.

5% (62/826) developed Cr ≥ 1.3 x BL and 20% (236/1182) discontinued TDF, including 66 (6%) who died. In multivariate analysis, factors associated with Cr ≥ 1.3 x BL were concomitant ddl (OR 2.14; p=0.015), BL CD4 (OR 1.59/ 100 cell decrement; p<0.0001), and female gender (OR 2.33;

p=0.029). Factors associated with TDF d/c were concomitant ddl (OR 2.21; p<0.0001), BL CD4 (OR 1.22/ 100 cell decrement; p<0.0001), and previous ARV exposure (OR 0.89/ 12 mo; p<0.0001). *Conclusions* Among patients taking TDF, Cr elevation and TDF discontinuation are associated with concomitant use of ddl (but not boosted PIs), and with lower CD4, as previously shown.

[PL5.4] The assessment of multi-locus gene effects upon lopinavir pharmacokinetics **A Owen, T Mahungu, C Cook, M Youle, M Johnson, D Back, S Khoo. University of Liverpool, UK; Royal Free Hospital, London, UK**

Purpose of the Study Variability in drug disposition is likely the cumulative result of multiple genetic and environmental effects. Standard methods for assessing multi-locus gene effects would be of clear advantage. We previously reported a cumulative scoring algorithm for nevirapine and have applied this methodology to lopinavir (LPV) pharmacogenetics. *Methods* 87 patients receiving LPV were included. Plasma LPV Cmin was sampled just before the next dose was due. Allelic discrimination was performed by real-time PCR for 9 SNPs from 6 loci (CYP2B6, CYP3A4, CYP3A5, MDR1, MRP1 and BCRP). Cmin were compared between different genotypes. Criteria for inclusion of SNPs/loci as 'susceptibility genes' were: i) P < 0.05, or ii) 0.05 < P < 0.10 with median [LPV] Cmin outside bioequivalence range (80-125%). LPV Cmins were then compared between patients with accumulating numbers of 'susceptibility genes' in the algorithm. *Summary of Results* CYP3A5*3 (A6986G), MDR1 (C3435T), MRP1 (G-260C) and BCRP (C421A) qualified for the algorithm. We observed a stepwise increase in median [LPV] Cmin with accumulating number of 'susceptibility' genes (N=87 patients: median [LPV] Cmin = 4915 ng/mL): 0 (N=16; 3427 ng/mL), 1 (N=38; 4419 ng/mL), 2 (N=11; 5183 ng/mL), 3 (N=15; 5777 ng/mL), 4 (N=9; 6998 ng/mL) [z = 2.5, P = 0.01 by Cuzick's trend test].



Conclusions These data are preliminary but suggest that cumulative scoring algorithms can be developed to assess multi-locus genetic effects influencing LPV pharmacokinetics. _____