O112  Enhanced normalisation of CD4/CD8 ratio with early antiretroviral therapy in primary HIV infection
Thornhil, J*; Inshaw, J; Oomeer, S; Kaleebu, P; Cooper, D; Ramjee, G; Schechter, M; Tambussi, G; Fox, J; Miro, J; Weber, J; Babiker, A; Porter, K; Fidler, S (London, UK)

O113  CD4+ cell count recovery in naïve patients initiating cART, who achieved and maintained plasma HIV-RNA suppression
Costagliola, D*; Lacombe, J; Ghosn, J; Delaugerre, C; Pialoux, G; Cuzin, L; Laruey, O; Merend, A; Trunchis, P; March-Krauss, M; Weiss, L; Delfraissy, J (Paris, France)

O114  Determinants of IL-6 levels during HIV infection
Borges, A*; O'Connor, J; Phillips, A; Rischbieth, F; Pett, S; Vjecha, M; French, M; Lundgren, J (London, UK)

O131  Efavirenz- but not nevirapine-based antiretroviral therapy decreases exposure to the levonorgestrel released from a subdermal contraceptive implant
Scarsi, K*; Lannorde, M; Daina, K; Dile Panchala, S; Else, L; Nakalema, S; Byakika-Kabwika, P; Khoo, S; Cohn, S; Mercy, C; Back, D (Omaha, USA)

O132  Darunavir pharmacokinetics throughout pregnancy and postpartum
Lambert, J*; Jackson, V; Else, L; Lawless, M; McDonald, G; Blanc, D; Patel, A; Stephens, K; Khoo, K (Dublin, Ireland)

O133  Does pregnancy increase the risk of ART-induced hepatotoxicity among HIV-positive women?
Huntington, J*; Thorne, C; Anderson, J; Newell, M; Taylor, G; Pilay, D; Hill, T; Tocksey, P; Sabir, C (London, UK)

O154  More virological failure with lamivudine than emtricitabine in efavirenz and nevirapine regimens in the Dutch nationwide HIV cohort
Rokx, C*; Flothu, A; van de Vijver, D; Verbon, A; Schutter, M; Gras, L; Rijnders, B (Rotterdam, The Netherlands)

O216  Predicted savings to the UK National Health Service from switching to generic antiretrovirals, 2014–2018
Hill, A*; Hill, T; Jose, S; Pozniak, A (Liverpool, UK)

O234  Regional differences in self-reported HIV care and management in the EuroSIDA study
Granborg Laut, K*; Mirocord, A; Lazarus, J; Reiss, P; Rockstroh, J; Karpov, I; Rukrmanov, A; Knyisz, B; Moreno, S; Gargalianos, P; Lundgren, J; Kirk, O; on behalf of EuroSIDA in EuroCoord (Copenhagen, Denmark)

O235  Major challenges in clinical management of TB/HIV co-infected patients in Eastern Europe compared with Western Europe and Latin America
Marie Elsen, A*; Schutte, A; Post, F; Panteleev, A; Fumur, H; Miller, R; Sakerin, A; Lasco, M; Tobias, J; Girardi, E; Miro, J; Bruyand, M; Obel, N; Caih, A; Prokilearea, D; Lundgren, J; Mocroft, A; Kirk, O; in EuroCoord TB/HIV Study Group (Copenhagen, Denmark)

O237  Large disparities in HIV treatment cascades between eight European and high-income countries – analysis of break points
Raymond, A*; Hill, A; Pozniak, A (London, UK)

O312  CD4 cell count and the risk of infective and non-infective serious non-AIDS events in HIV-infected persons seen for care in Italy
Maderdola, G*; d'Alimino Monforte, A; Girardi, E; Di Biagio, A; Lo Caputo, S; Ploini, R; Marchetti, G; Pelisser, G; Giacometti, A; Galli, L; Antonini, A; Cozzi Lepri, A; on behalf of ICONA Foundation Study (Sassari, Italy)

O314  Effects of age on symptom burden, mental health and quality of life amongst people with HIV in the UK
McGowan, J*; Rice, J; Rodiger, A; Fisher, M; Miners, A; Johnson, M; Ellwood, J; Collins, S; Hart, G; Phillips, A; Speakman, A; Lampe, F (London, UK)

O315  Lack of association between use of efavirenz and death from suicide: evidence from the D:A:D study
Smith, C*; Ryom, L; d'Alimino Monforte, A; Reiss, P; Mocroft, A; El-Sadr, W; Weiler, R; Law, M; Sabir, C; Lundgren, J (London, UK)

O322  A clinically useful risk-score for chronic kidney disease in HIV infection
Mocroft, A*; Lundgren, J; Ross, M; Law, M; Reiss, P; Kirk, O; Smith, C; Wentworth, D; Heuhaus, J; Fux, C; Moranne, O; Montal, P; Johnson, M; Ryom, L (London, UK)

*Indicates presenting author.
O324 Gender differences in HIV-positive persons in use of cardiovascular disease-related interventions: D:A:D study
Ingrid Hafstein, C*; Pyron, L; El-Gadi, W; Mocroft, A; Reiss, P; de Wit, S; Dabis, F; Pradier, C; d’Arminio Monforte, A; Rickenbach, M; Law, M; Lundgren, J; Sabin, C (Copenhagen, Denmark)

O332 The R263K mutation in HIV integrase that is selected by dolutegravir (DTG) may actually prevent clinically relevant resistance to this compound
Wainberg, M*; Anstett, K; Mesplede, T; Quashe, P; Han, Y; Oliveira, M (Montreal, Canada)

O334 Genotypic tropism testing in proviral DNA to guide maraviroc initiation in aviremic subjects: 48-week analysis of the PROTEST study
García, F; Poveda, E; Jesús Pérez-Elias, M; Hernández Quero, J; Ángeles Ribas, M; J. Martínez-Madrid, O; Flores, J; Crespo, M; Gutiérrez, F; García-Delclos, M; Imaz, A; Ocampo, A; Artero, A; Blanco, F; Bernal, E; Pasqual, J; Mínguez-Gallego, C; Pérez, N; Aiestarán, A; Pareades, R* (Barcelona, Spain)

O421 Efavirenz (EFV) 400mg daily remains non-inferior to 600mg: 96 week data from the double-blind, placebo-controlled ENCORE study
Carey, D* (Sydney, Australia)

O422 Effectiveness of a reduced dose of efavirenz plus 2 NRTIs as maintenance antiretroviral therapy with the guidance of therapeutic drug monitoring
Yang, S-P; Lu, W-C; Lee, K-Y; Wu, B-R; Su, Y-C; Wu, P-Y; Zhang, J-Y; Luo, Y-Z; Sun, H-Y; Chang, S-Y; Lin, S-W; Hung, C-C* (Taipei City, Taiwan)

O423A The PROTEa trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV-1 RNA below 50 copies/mL
Antinori, A*; Ambas, J; Fehr, J; Girardi, P-M; Horban, A; Hill, A; van Deuff, Y; Moccklinghoff, C; Hill, A (Rome, Italy)

O423B Analysis of neurocognitive function and CNS endpoints in the PROTEA trial: darunavir/ritonavir with or without nucleoside analogues
Clenn, A*; Johanssen, V; Gerstott, J; Ciotet, B; Ripamonti, D; Murungi, A; Bicer, C; Hadasek, M; Moccklinghoff, C (Brighton, UK)

O424 Rate of viral load failure over time in people on ART in the UK Collaborative HIV Cohort (CHIC) study
O’Connor, J*; Smith, C; Lampe, F; Johnson, M; Sabin, C; Phillips, A (London, UK)

O432A HIV-1 attachment inhibitor prodrug BMS-663068 in antiretroviral-experienced subjects: week 24 subgroup analysis
Brinson, C; Lalezari, J; Latiff, G; Thompson, M; Echevarría, J; Treviño-Pérez, S; Stock, D; Joshi, S; Hanna, G; Latallade, M* (Wallingford, USA)

O432B Safety profile of HIV-1 attachment inhibitor prodrug BMS-663068 in antiretroviral-experienced subjects: week 24 analysis
Lalezari, J; Latiff, G; Brinson, C; Echevarría, J; Treviño-Pérez, S; Bogner, J; Stock, D; Joshi, S; Hanna, G; Latallade, M* (Wallingford, USA)

O434 48-week efficacy and safety and early CNS tolerability of doravirine (MK-1439), a novel NNRTI, with TDF/FTC in ART-naive HIV-Infected patients
Gatek, J; Morales-Ramirez, J; Higra, D; Thompson, M; Kaikawas, A; Hoffmann, C; Rujina, S; Olsyem, O; Escorl, S; Dretler, R; Harvey, C; Xu, X; Toppler, H (Barcelona, Spain)

*Indicates presenting author.
Enhanced normalisation of CD4/CD8 ratio with early antiretroviral therapy in primary HIV infection

Authors: J Thornhill1, J Inshaw2, S Oomeer1, P Kaleebee1, D Cooper4 G Ramjee5, M Schechter4, G Tambussi1, JFoyle1, JM Miro1, J Weber2 A Babiker2, K Porter2 and Sarah Fidler1

1Department of Medicine, Imperial College London, UK. 2MRC Clinical Trials Unit at UCL, Institute of Clinical Trials & Methodology, London, UK. 3MRC, Uganda Virus Research Institute, Kampala, Uganda. 4Virchow Institute, University of New South Wales, Sydney, Australia. 5HIV Prevention Unit, MRC, Durban, South Africa. 6Hospital Escola Sao Francisco de Assis, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil. 7Division of Infectious Diseases, Ospedale San Raffaele, Milan, Italy. 8Days and St Thomas’ NHS Trust, Kings College London, London, UK. 9Hospitaill Clinic, University of Barcelona, Spain.

Introduction

Despite normalization of total CD4 counts, ongoing immune dysfunction is noted amongst those on antiretroviral therapy (ART). Low CD4/CD8 ratio is associated with a higher risk of AIDS and non-AIDS events and may act as a marker of immune senescence [1]. This ratio is improved by ART although normalization is uncommon (6-26%) [2]. The probability of normalization of CD4 count is improved with immediate ART initiation in primary HIV infection (PHI) [3]. We examined whether CD4/CD8 ratio similarly normalized in early (within 6 months) vs. late ART at PHI.

Methods

Using data from the SPARTAC trial and the UK Register of HIV Seroconverters (UKR), we used cox proportional hazard models to examine the effect of ART with time (continuous) from HIV seroconversion (SC) on CD4/CD8 ratio (>1.0) adjusted for sex, risk group, ethnicity, enrolment from an African site and both CD4 count and age at ART initiation. We also examined that effect by dichotomizing HIV duration at ART initiation (ART started within six months of SC: early ART; ART initiated > six months after SC: late). A normal CD4/CD8 T-cell ratio was defined as ≥ 1.0. Primary HIV infection was defined as per the UKR [3] and SPARTAC [5] protocols and an Estimated Date of SC calculated as per these protocols. As a secondary analysis, Cox proportional hazards models were used to examine the effect of CD4/CD8 ratio at HIV seroconversion on time to initiation of ART or CD4 count <350 cells/mm³ in those individuals with CD4>350 cells/mm³ at seroconversion. We fitted two Cox models, one with CD4/CD8 ratio at HIV seroconversion as a continuous variable and one with the CD4/CD8 ratio dichotomised (<0.5, 0.5-1.0, 1.0).

Results

482/573 (84%) of individuals presenting with PHI had abnormal CD4/CD8 ratios at seroconversion. Overall median [95%CI] time to normalization of CD4/CD8 ratio was 715 [408, 988] days. For those initiating ART < 6 months (early ART) 172 [117, 280] days, and 1344 [1060, 1630] days for those initiating ART > 6 months (late ART). Individuals who started early ART were significantly more likely to normalize the CD4/CD8 ratio (aHR [95%CI]=2.47 [1.67, 3.67], p<0.001) compared to those starting late ART (see figure 1). Within one year from the date of starting ART: 129/275 (46.9%) individuals in the early group normalized the CD4/CD8 ratio, compared with 161/127 (12.6%) in the late group. The affect of time (continuous) showed a significant association between months from estimated date to ART initiation and CD4/CD8 ratio normalization (HR [95%CI]=0.08 [0.97, 0.99], p<0.001) which implies for every month delay there was a reduction in probability of normalization of CD4/CD8 ratio by 2%. A sensitivity analysis performed at a CD4/CD8 ratio of 1.2 was qualitatively unchanged.

Figure 1. Kaplan Meier: Time from ART Initiation to Normalisation of CD4/CD8 ratio

268 individuals were eligible for the secondary analysis (SCc Spartac plus UKR participants), with baseline CD4 counts > 350 cells/mm³. The median time to ART initiation or CD4 < 350 cells was 1.51 [95%CI 1.32, 2.37] years. Higher CD4/CD8 ratio at seroconversion was associated with longer time to ART initiation (aHR [95% CI]=0.32 [0.20, 0.51], p<0.001). CD4/8 ratios at seroconversion were categorized into three groups; (<0.5, 0.5-1.0, >1.0), see figure 2. Compared with those individuals with CD4/8 ratio >1, the lower the CD4/8 ratio groups had a greater risk of reaching CD4 count < 350 or starting long-term ART.

Figure 2. Kaplan Meier: Time to CD4>350 or ART initiation according to CD4/CD8 ratio group at SC

Conclusions

Higher CD4/CD8 ratio may reflect a more “normal” immune phenotype conferring enhanced prognosis. In this large cohort the likelihood of achieving normalization of CD4/CD8 ratios was increased for each month closer to SC ART was initiated. Higher CD4/CD8 ratio at SC (in those with CD4 count >350) was associated with faster disease progression suggesting that CD4/CD8 ratio may assist in determining the optimal time of ART initiation in PHI.

References

Background: A key objective of combined antiretroviral therapy (cART) is to reach and maintain high CD4 cell counts to provide long-term protection against AIDS defining opportunistic infections and malignancies, as well as other comorbidities.

Objectives:
✓ To assess CD4 + cell count recovery up to 7 years in naïve patients initiating cART with at least three drugs in usual clinical care.
✓ To examine patients’ baseline characteristics associated with achieving CD4 > 500 cells/mm³.

Methods: From the French Hospital Database on HIV (ANRS CO4), we selected ART naïve individuals initiating cART from 2000 with at least 2 years of follow-up. Participants were further required to have achieved viral load (VL) suppression by 9 months after initiating cART and were censored in case of virological failure (VF). We calculated the proportion of patients (Kaplan-Meier estimates) who achieved CD4 recovery defined as CD4 >500 cells/mm³ according to baseline CD4 cell count. Multivariable Cox’s proportional hazards models were used to assess baseline characteristics associated with CD4 recovery.

Results: 13 912 patients were enrolled in the study with a median follow-up on ART without virological failure of 50.1 months (IQR: 30.8-80.0). At cART initiation, the median age was 38.7 years (IQR: 32.3-46.1) and 8976 (64.5 %) were men.

Baseline characteristics

<table>
<thead>
<tr>
<th>Median CD4 [IQR]</th>
<th>Baseline CD4</th>
<th>1 year</th>
<th>2 years</th>
<th>3 years</th>
<th>4 years</th>
<th>5 years</th>
<th>6 years</th>
<th>7 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4=200 (n=5909)</td>
<td>8% (140-150)</td>
<td>38% (220-230)</td>
<td>66% (230-240)</td>
<td>91% (240-250)</td>
<td>94% (250-260)</td>
<td>96% (260-270)</td>
<td>97% (270-280)</td>
<td></td>
</tr>
<tr>
<td>CD4=300 (n=5751)</td>
<td>40% (260-270)</td>
<td>81% (280-290)</td>
<td>87% (290-300)</td>
<td>91% (300-310)</td>
<td>94% (310-320)</td>
<td>95% (320-330)</td>
<td>97% (330-340)</td>
<td></td>
</tr>
<tr>
<td>CD4=400 (n=500)</td>
<td>74% (270-280)</td>
<td>95% (300-310)</td>
<td>97% (310-320)</td>
<td>98% (320-330)</td>
<td>99% (330-340)</td>
<td>99% (340-350)</td>
<td>99% (350-360)</td>
<td></td>
</tr>
</tbody>
</table>

Factors associated with CD4 recovery (CD4>500/mm³): Multivariable analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR [IC 95%]</th>
<th>HR [IC 95%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td>0.98 [0.91-1.05]</td>
<td>0.95 [0.89-1.01]</td>
</tr>
<tr>
<td>Men IDU</td>
<td>0.87 [0.71-1.05]</td>
<td>0.81 [0.66-0.98]</td>
</tr>
<tr>
<td>Men heterosexual</td>
<td>0.80 [0.73-0.87]</td>
<td>0.79 [0.73-0.85]</td>
</tr>
<tr>
<td>Men other</td>
<td>0.81 [0.73-0.90]</td>
<td>0.77 [0.69-0.85]</td>
</tr>
<tr>
<td>Women IDU</td>
<td>0.87 [0.71-1.05]</td>
<td>0.81 [0.66-0.98]</td>
</tr>
<tr>
<td>Women heterosexual</td>
<td>0.97 [0.89-1.04]</td>
<td>0.93 [0.85-1.01]</td>
</tr>
<tr>
<td>Women other</td>
<td>0.97 [0.86-1.09]</td>
<td>0.92 [0.82-1.04]</td>
</tr>
<tr>
<td>Age at baseline:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15-29 years</td>
<td>0.98 [0.81-1.20]</td>
<td>0.89 [0.72-1.10]</td>
</tr>
<tr>
<td>30-39 years</td>
<td>1.01 [0.84-1.20]</td>
<td>0.92 [0.74-1.13]</td>
</tr>
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<td>40-49 years</td>
<td>0.98 [0.82-1.17]</td>
<td>0.87 [0.71-1.06]</td>
</tr>
<tr>
<td>50-59 years</td>
<td>0.96 [0.81-1.15]</td>
<td>0.86 [0.71-1.05]</td>
</tr>
<tr>
<td>≥ 60 years</td>
<td>0.99 [0.85-1.15]</td>
<td>0.93 [0.77-1.10]</td>
</tr>
<tr>
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<td></td>
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<tr>
<td>Other</td>
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<td>1.00 [0.83-1.20]</td>
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<td>Subsahelian</td>
<td>0.87 [0.69-1.09]</td>
<td>0.87 [0.70-1.08]</td>
</tr>
<tr>
<td>HCV antibody negative</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>0.85 [0.68-1.06]</td>
<td>0.85 [0.68-1.06]</td>
</tr>
<tr>
<td>Time since diagnosis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>1.07 [1.02-1.12]</td>
<td>1.07 [1.02-1.12]</td>
</tr>
<tr>
<td>≥ 1 year</td>
<td>1.00 [1.00-1.00]</td>
<td>1.00 [1.00-1.00]</td>
</tr>
</tbody>
</table>

Conclusions: This study shows that CD4 cell counts continue to increase 7 years after cART initiation, whatever the baseline CD4 cell count. Failing to achieve CD4 recovery with continuous viral load suppression is rare for naïve patients initiating cART in routine clinical practice, but takes substantially longer in patients who initiate antiretroviral therapy at low CD4 cell counts. Higher VL and CD4 before cART initiation, as well as younger age, initiating with 2 NRTI + 1 INI and during primary infection were associated with a better CD4 recovery.
Factors associated with IL-6 levels during HIV infection

Álvaro Borges1, J L O’Connor2, AN Phillips3, FF Rönnholm4, S Pett2,4,5, MJ Vjecha6, MA French7,8, JD Lundgren1, for the INSIGHT SMART and ESPRIT Study Groups and the SILCAAT Scientific Committee

1CHIP, Department of Infectious Diseases and Rheumatology, Section 2100, Rigshospitalet – University of Copenhagen; 2 Research Dep of Infection and Population Health, UCL, London, UK; 3 Dep of Infectious Diseases and Rheumatology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; 4 MRC Clinical Trials Unit, UCL, London, UK; 5 Kirby Institute, University of New South Wales Australia, Sydney, Australia; 6 Institute for Clinical Research, Inc., Veterans Affairs Medical Center, Washington, DC, USA; 7 School of Pathology and Laboratory Medicine, University of Western Australia, Perth, Australia; 8 Dep of Clinical Immunology, Royal Perth Hospital and PathWest Laboratory Medicine, Perth, Australia

INTRODUCTION

• Interleukin-6 (IL-6) is a pro-inflammatory cytokine that regulates various pathophysiological processes.1
• Elevated plasma IL-6 levels have been linked to cardiovascular disease (CVD), cancer and death.2,3,4
• Compared to the general population, treated HIV+ persons have higher IL-6,5 but few data on the factors associated with IL-6 levels currently exist.

STUDY AIM

To identify factors independently associated with IL-6 during HIV infection

MATERIAL AND METHODS

SMART:6 RCT that compared, in 5,472 individuals with CD4+ > 350 cells/mm3 at baseline, continuous use of ART with structured treatment interruption guided by CD4+ count

ESPRIT:7 RCT that compared IL-2 plus ART with ART alone in 4,111 individuals with CD4+ > 300 cells/mm3

SILCAAT:7 RCT that compared IL-2 plus ART with ART alone in 1,695 individuals with CD4+ between 50 and 299 cells/mm3

Inclusion Criteria:
All SMART, ESPRIT and SILCAAT participants whose serum IL-6 levels were measured at baseline (N=9,864).

STATISTICAL ANALYSES

Independent factors associated with IL-6 levels were identified by multivariable linear regression models. Log2 transformed IL-6 levels were used as the dependent variable. Fold differences (FDs) with 95% CI in IL-6 levels per unit or category difference in the covariates were calculated to assess the contribution of baseline variables to the variance of IL-6.

The regression models were fitted to three different datasets:
(1) SMART, ESPRIT and SILCAAT (N=9,864): age, gender, ethnicity, BMI, CD4+ cell counts (nadir and baseline), markers of inflammation (hsCRP) and activated coagulation (D-dimer), antiretroviral therapy (ART) use and ART regimens;
(2) SMART and ESPRIT (N=6,938): co-morbidities (HBV, HCV, diabetes mellitus, cardiovascular disease) and renal function (eGFR);
(3) SMART participants only (N=4,498): smoking, level of education (less than high school, high school and bachelor’s degree or above), triglycerides and cholesterol levels (LDLc and HDLc).

As different central laboratories were used, terms for each study were entered in all models.

RESULTS

• Demographics independently correlated with higher IL-6 levels were older age, higher BMI and lower educational level (Fig 1).
• Regarding HIV-specific factors, higher HIV RNA was associated with higher IL-6, while higher nadir CD4+ was associated with lower IL-6 (Fig 2).
• Among those on ART, PI-based regimens were independently related to higher IL-6 levels than NNRTI-based regimens (Fig 3). This was a drug class effect and all individual PI drugs were associated with higher IL-6 when compared to efavirenz. Nevirapine use was associated with lower IL-6 levels.
• hsCRP and D-dimer were positively correlated with IL-6 (data not shown).
• Smoking and all the co-morbidities investigated were found to be associated with higher IL-6 (Fig 4).
• Higher eGFR values at baseline were associated with lower IL-6. Both higher LDLc and higher HDLc were associated with lower IL-6 (data not shown).

CONCLUSIONS

• Higher IL-6 levels in HIV patients were associated with older age and non-black race, higher BMI and lower serum lipids, ongoing HIV replication, low nadir CD4 counts, comorbidities and decreased renal function.
• PI use was also associated with higher IL-6 while nevirapine use was associated with lower IL-6.
• The enhanced inflammation seen during HIV infection is probably determined by a synergistically deleterious interaction of HIV-related and -unrelated morbidity.

REFERENCES
Efavirenz- but not nevirapine-based antiretroviral therapy decreases exposure to the levonorgestrel released from a subdermal contraceptive implant

Kimberly Scarsi1, Mohammed Lamorde2, Kristin Darin2, Sujan Dilly Panchala4, Laura Else4, Shadia Nakalema2, Pauline Byakika-Kibwika2, Saye Khoo3, Susan Cohn4, Concepta Merry4, David Back4

1University of Nebraska Medical Center, Omaha, USA; 2Makere University College of Health Sciences, Infectious Diseases Institute, Kampala, Uganda; 3Northwestern University, Chicago, USA; 4University of Liverpool, Liverpool, UK; 5Trinity College Dublin, Dublin, Ireland

ABSTRACT

Background: Subdermal contraceptive implants, such as levonorgestrel (LNG) implants, are a safe and effective form of long-acting contraception, but their use among HIV-infected women on antiretroviral therapy (ART) may be contraindicated given the potential for a cytochrome P450 (CYP) mediated drug-drug interaction. Our study aimed to characterize the pharmacokinetics of levonorgestrel released from a subdermal implant over 6 months in HIV-infected Ugandan women on nevirapine (NVP) or efavirenz (EFV)-based ART.

Material and Methods: The non-randomized, parallel group study compared LNG pharmacokinetics between HIV-infected Ugandan women not eligible for ART (control group, n=12) and those on stable NVP- (n=20) or EFV (n=20)-based ART. LNG concentrations were assessed using a validated LC-MS/MS method, with an assay calibration range of 50-1500 pg/mL, within normalizing for body weight (50-62% decrease). Women in the control group had higher baseline LNG concentrations (50-62% lower than women on NVP or EFV). Women on NVP or EFV had stable LAN concentrations over 6 months, with a difference partially explained by body weight. These data support use of the LNG implant with NVP-based ART.

RESULTS

• 20 subjects were enrolled into each study arm: 18 (Control group), 20 (NVP group) and 20 (EFV group) subjects met the primary endpoint (month 6 visit) and are included in the analysis
• 3 subjects (Control group) discontinued the implant early: o Pregnancy was detected at week 1 visit (n=1) o Met ART eligibility criteria at month 3 visit (n=1) o Implant removed between entry and week 1 visit (n=1)
• Subject demographics at enrolment are described in Table 1.

CONCLUSIONS

• LNG concentrations were reduced by 40-54% in women receiving EFV-based ART, beginning as early as 1 week post-insertion.
• The extent of this drug-interaction is more pronounced after normalizing for body weight (50-62% decrease).
• Conversely, women on NVP-based ART had consistently higher LNG concentrations (32-39%).

METHODOLOGY

Exclusion Criteria:
- Hemoglobin < 9 g/dL, creatinine > 2.5-times upper limit of normal (ULN) or alanine transaminase (ALT) > 5-times ULN at screening
- Women B and C only: HIV-1 RNA > 400 copies/mL at screening
- Use of drugs with known drug interactions with LNG (all subjects)
- NVP or EFV (ART groups only) ≤ 30 days of study entry
- A two-rod (75 mg/ml) LNG implant was placed subdermally in the upper arm of each study enrolment (day 0)

Pharmacokinetic analysis:
- Sampling for LNG analysis was obtained pre-implant and at weeks 4, 12, and 24 post-insertion (Figure 1)
- LNG plasma concentrations were analyzed using a validated LC-MS/MS method with an assay calibration range of 50-1500 pg/mL
- Safety monitoring (e.g. pregnancy test, adverse events) and family planning counseling were performed at each study visit.

RESULTS

• 20 subjects per group were enrolled to detect a 45% change in LNG concentrations between groups; power = 0.9 and alpha = 0.05, allowing for a 20% attrition (16 per group)
• Within group LNG concentrations are summarized for each time point using geometric mean (GM) with 90% confidence intervals (CI); between group comparisons are reported as GM ratio (NVP vs control and EFV vs control) with 90% CI.
• Subject demographics were described as mean ± standard deviation (SD) and compared by ANOVA, followed by a student’s t-test as need to assess between group differences.
• Linear regression was used to evaluate the impact of body weight on LNG concentration, controlling for ART use and study visit.

REFERENCES

1. Providing informed consent to participate in the study. Desired to use the LNG subdermal implant for contraception.
2. Recently, efavirenz-based ART was found to significantly reduce (by 30-50%) efavirenz-mediated drug-drug interaction. Our study aimed to characterize the pharmacokinetics of levonorgestrel released from a subdermal implant over 6 months in HIV-infected Ugandan women on nevirapine (NVP) or efavirenz (EFV)-based ART.

Background:
Subdermal contraceptive implants, such as levonorgestrel (LNG) implants, are a safe and effective form of long-acting reversible contraception. Although recommended by the WHO and widely used among HIV-infected women, there is growing concern for reduced contraceptive efficacy with their combined use. In contrast, these data support use of the LNG implant with NVP-based ART.

Methods:
A non-randomized, parallel group study compared LNG pharmacokinetics between HIV-infected Ugandan women not eligible for ART (control group, n=12) and those on stable NVP- (n=20) or EFV (n=20)-based ART. LNG concentrations were assessed using a validated LC-MS/MS method, with an assay calibration range of 50-1500 pg/mL, within normalizing for body weight (50-62% decrease). Women in the control group had higher baseline LNG concentrations (50-62% lower than women on NVP or EFV). Women on NVP or EFV had stable LNG concentrations over 6 months, with a difference partially explained by body weight. These data support use of the LNG implant with NVP-based ART.

Results:
20 subjects per group were enrolled to detect a 45% change in LNG concentrations between groups; power = 0.9 and alpha = 0.05, allowing for a 20% attrition (16 per group).
Within group LNG concentrations are summarized for each time point using geometric mean (GM) with 90% confidence intervals (CI); between group comparisons are reported as GM ratio (NVP vs control and EFV vs control) with 90% CI.
Subject demographics were described as mean ± standard deviation (SD) and compared by ANOVA, followed by a student’s t-test as need to assess between group differences.
Linear regression was used to evaluate the impact of body weight on LNG concentration, controlling for ART use and study visit.

Conclusion:
LNG concentrations were reduced by 40-54% in women receiving EFV-based ART, beginning as early as 1 week post-insertion.
The extent of this drug-interaction is more pronounced after normalizing for body weight (50-62% decrease).
Conversely, women on NVP-based ART had consistently higher LNG concentrations (32-39%).
This increase was less pronounced after normalizing for body weight (16-21%).
Antiretroviral therapy is recommended during pregnancy for prevention of mother-to-child transmission (MTCT) of HIV. Physiological changes during pregnancy are known to affect the pharmacokinetics (PK) of protease inhibitors (PI), leading to lower exposures in pregnant women. Here we examine the PK of DRV/r 800/100 mg once daily (OD) over the course of pregnancy and postpartum.

**Subjects**
In this prospective open labelled study, pregnant HIV-positive women received standard dosing of DRV/r (800/100 mg od) as part of their routine antenatal care. Women attending the Antenatal Infectious Diseases Clinic of the Rotunda Hospital, Dublin were recruited between August 2009 and December 2013.

**Study design**
DRV plasma trough concentrations [DRV] were determined in the first (T1) and/or second (T2) and/or third (T3) trimester and postpartum (PP) using a validated HPLC-MS/MS methodology; LLQ 78.1 ng/mL (Lab21, Cambridge UK). Where possible paired maternal and cord blood samples were taken at delivery.

**RESULTS:**

**Maternal Characteristics**
To date 20 women (12 black African, 8 Caucasian) have been enrolled. Median (range) baseline CD4 count was 338 cells/µL (108-715) and median baseline plasma viral load was 555 copies/mL (<40-618894). All but 2 women were virally suppressed at time of delivery (114 and 176 copies/mL; 1 subtherapeutic at T3) and median CD4 count was 410 cells/µL (92-947). Baseline demographics are presented in Table 1.

**Comparison of Maternal & Cord DRV Concentration**
Maternal and cord [DRV] were available for 10 mother-baby pairs. Median maternal [DRV] at the time of delivery was 1668 ng/mL (607-5528), while median cord [DRV] was 254 ng/mL (<LLQ-745). This variation is most likely attributable to the differences in time since last dose. The median ratio of cord blood-to-maternal ratio was 0.11 (0.06-0.49).

**Birth Outcomes**
There were 20 livebirths, all term deliveries and there were no cases of MTCT.

**CONCLUSIONS:**
In most cases examined, DRV/r (800/100 mg OD) was effective at achieving adequate therapeutic drug levels (>550 ng/mL) during pregnancy. However, reduced DRV plasma concentrations in the second/third trimesters, highlights the need for TDM in this population, and warrants further study of pregnancy-associated changes in DRV pharmacokinetics. The transplacental transfer of DRV reported here is low, and consistent with previous reports [1]. Further investigation in a larger cohort should be carried out.

**REFERENCES**
Does pregnancy increase the risk of ART-induced hepatotoxicity among HIV-positive women?

S Huntington1,2, C Thorne1, J Anderson3, ML Newell5, G P Taylor7, D Pillay8, T Hill9, P Tookey1, C Sabin1

1. Imperial College Healthcare NHS Trust, London
2. School of Medicine, University College London, London
3. UCL Medical School and The Mortimer Market Centre, London
4. King’s College London, London
5. UCL Medical School and The National Institute for Health Research Biomedical Research Centres, London
6. The Abdala-Belaisch Institute for Infectious Diseases and Epidemiology Research, University of Natal, Durban, South Africa
7. North Middlesex University Hospital NHS Trust, London
9. University of North Carolina, Chapel Hill, USA

Correspondence: susan.huntington.09@ucl.ac.uk

Background

- High rates of hepatotoxicity have been observed among HIV-positive pregnant women on antiretroviral therapy (ART).
- The liver enzyme alanine aminotransferase (ALT) can be used as a biomarker, with elevated levels suggesting hepatotoxicity.
- Cross-sectional studies comparing the rate of liver enzyme elevation (LEE) in pregnant and non-pregnant HIV-positive women have generated conflicting results. Some studies found that pregnancy increased the risk of LEE whilst others did not.

Aim

To assess whether pregnancy is associated with an increased risk of LEE.

Materials and Methods

Data source

Combined data from the UK Collaborative HIV Cohort (UK CHIC) study and the UK and Ireland National Study of HIV in Pregnancy and Childhood (NSHPC) were used. The UK CHIC study is a multinational observational cohort study of HIV-positive adult participants attending one of the 19 collaborating centres for HIV care (www.ukchic.org.uk). The NSHPC is an observational active surveillance study of HIV-positive women accessing antenatal care in all maternity units in the UK and Ireland (www.ucl.ac.uk/nsnhpc).

Inclusion criteria

Women starting ART in 2000-2012 aged 16-49 years with ≥1 ALT measurement available whilst on ART were included irrespective of pregnancy status at ART start. Women with severe LEE (<5 times the upper limit of normal (ULN)) were excluded (n=10).

Primary outcome

ALT was assessed according to the Division of AIDS toxicity guidelines1 to identify factors associated with LEE (Grade 1-4). LEE was defined as ≥2.5 times the ULN in women with no evidence of LEE at baseline (n=511) or ≥2.25 times the baseline ALT among women with ALT-ULN at baseline (n=304).

Statistical methods

Cox proportional hazards were used to assess the associations between fixed and time-dependent factors and the risk of incident LEE. Women could contribute data when they were pregnant and when they were not pregnant, thereby acting as their own controls.

Table 1: Characteristics of 3815 HIV-positive women starting ART in 2000-2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>34 (29.9)</td>
</tr>
<tr>
<td>Exposure group</td>
<td></td>
</tr>
<tr>
<td>Heterosexual sex</td>
<td>3456 (90.6)</td>
</tr>
<tr>
<td>Injecting drug use</td>
<td>122 (3.2)</td>
</tr>
<tr>
<td>Other/not known</td>
<td>237 (6.2)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Black-African</td>
<td>2517 (66.0)</td>
</tr>
<tr>
<td>White</td>
<td>651 (17.1)</td>
</tr>
<tr>
<td>Other/not known</td>
<td>647 (17.0)</td>
</tr>
<tr>
<td>Hepatitis B/C co-infection</td>
<td>317 (8.3)</td>
</tr>
<tr>
<td>Year of starting ART</td>
<td></td>
</tr>
<tr>
<td>2000-2005</td>
<td>1813 (47.5)</td>
</tr>
<tr>
<td>2006-2014</td>
<td>2002 (52.5)</td>
</tr>
<tr>
<td>Time since HIV-diagnosis</td>
<td></td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>1460 (38.3)</td>
</tr>
<tr>
<td>3–12 months</td>
<td>151 (37.1)</td>
</tr>
<tr>
<td>≥12 months</td>
<td>1740 (44.7)</td>
</tr>
<tr>
<td>CD4 count (cells/mm³)</td>
<td></td>
</tr>
<tr>
<td>&lt;250</td>
<td>251-350</td>
</tr>
<tr>
<td>≥350</td>
<td>556 (20.2)</td>
</tr>
<tr>
<td>Viral load (copies/ml)</td>
<td></td>
</tr>
<tr>
<td>≤100,000</td>
<td>2142 (73.3)</td>
</tr>
<tr>
<td>&gt;100,000</td>
<td>779 (26.7)</td>
</tr>
<tr>
<td>Pregnancy status when starting ART</td>
<td></td>
</tr>
<tr>
<td>Not pregnant</td>
<td>3274 (85.8)</td>
</tr>
<tr>
<td>≥20 weeks gestation</td>
<td>208 (5.5)</td>
</tr>
<tr>
<td>≥20 weeks gestation</td>
<td>333 (8.7)</td>
</tr>
<tr>
<td>Type of ART regimen</td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td>2134 (55.9)</td>
</tr>
<tr>
<td>PI</td>
<td>1176 (30.8)</td>
</tr>
<tr>
<td>NRTI</td>
<td>130 (3.4)</td>
</tr>
<tr>
<td>Other</td>
<td>357 (9.8)</td>
</tr>
</tbody>
</table>

Variables associated with LEE

- After adjusting for other factors associated with LEE, pregnancy was associated with a 1.66-fold increase in a woman’s risk of LEE (Table 2).
- Other factors independently associated with increased risk of LEE were lower CD4 count, HBV/HCV co-infection, having acquired HIV via injecting drug use, calendar year, use of efavirenz and use of nevirapine.
- Use of zidovudine was associated with decreased risk of LEE as was increasing time on an NNRTI-based regimen.
- Pregnancy status, CD4 count and viral load when starting ART were not associated with LEE.

Table 2: Unadjusted and adjusted Cox proportional hazards regression analyses to identify factors associated with the incidence of LEE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted HAZ (95% CI)</th>
<th>Adjusted HAZ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant at ART start</td>
<td>1.38 (1.1, 1.7)</td>
<td>1.66 (1.3, 2.1)</td>
</tr>
<tr>
<td>Pregnant experienced ART</td>
<td>1.05 (0.9, 1.2)</td>
<td>-</td>
</tr>
<tr>
<td>Age (per 10 year increase)</td>
<td>1.00 (0.9, 1.1)</td>
<td>1.05 (1.0, 1.1)</td>
</tr>
<tr>
<td>Route of exposure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual sex</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Injecting drug use</td>
<td>2.60 (2.0, 3.4)</td>
<td>1.55 (1.1, 2.2)</td>
</tr>
<tr>
<td>Other/not known</td>
<td>1.02 (0.8, 1.3)</td>
<td>0.93 (0.7, 1.2)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black-African</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>White</td>
<td>1.37 (1.2, 1.6)</td>
<td>1.17 (1.0, 1.4)</td>
</tr>
<tr>
<td>Other/not known</td>
<td>1.09 (0.9, 1.3)</td>
<td>1.08 (0.9, 1.3)</td>
</tr>
<tr>
<td>Calendar year (per 1 year increase)</td>
<td>1.06 (1.0, 1.1)</td>
<td>1.05 (1.0, 1.1)</td>
</tr>
<tr>
<td>CD4 count (cells/mm³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥250</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>251-350</td>
<td>0.85 (0.7, 1.0)</td>
<td>0.82 (0.7, 1.0)</td>
</tr>
<tr>
<td>≥350</td>
<td>0.88 (0.7, 1.1)</td>
<td>0.83 (0.7, 1.0)</td>
</tr>
<tr>
<td>ART drug in regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine</td>
<td>0.68 (0.6, 0.8)</td>
<td>0.73 (0.6, 0.9)</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>1.00 (0.9, 1.1)</td>
<td>1.26 (1.1, 1.5)</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>1.02 (0.9, 1.2)</td>
<td>1.54 (1.3, 1.9)</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>1.88 (1.3, 3.3)</td>
<td>-</td>
</tr>
<tr>
<td>Duration on ART (per additional year)</td>
<td>1.03 (1.0, 1.1)</td>
<td>-</td>
</tr>
<tr>
<td>Duration on PI regimen</td>
<td>1.07 (1.0, 1.1)</td>
<td>-</td>
</tr>
<tr>
<td>Duration on NNRTI regimen</td>
<td>0.94 (0.9, 1.0)</td>
<td>0.90 (0.9, 1.0)</td>
</tr>
<tr>
<td>Duration on NRTI regimen</td>
<td>1.10 (1.0, 1.2)</td>
<td>-</td>
</tr>
</tbody>
</table>

Discussion

Pregnancy was associated with a 1.66-fold increase in a woman’s risk of LEE.

Limitations

- In pregnancy, LEE could be a result of obstetric complications such as pre-eclampsia rather than ART-related hepatotoxicity. However, the rate of LEE was higher than would be anticipated due to obstetric complications (1%).
- ALT is monitored more closely in groups at risk of hepatopathy which could lead to an over-estimate of LEE incidence.

Conclusion

Our study provides further evidence that pregnancy poses an increased risk for LEE among women on antiretroviral therapy. This finding highlights the importance of close monitoring of liver biomarkers and clinical symptoms of toxicity during antenatal care.

References

Increased Virological Failure with Lamivudine Compared to Emtricitabine in Combination with Tenofovir and Efavirenz or Nevirapine in the Dutch ATHENA Cohort.

Background
Lamivudine and emtricitabine are equally recommended with tenofovir-DF and efavirenz or nevirapine as first line cART for ART naive HIV-1 patients. The use of generic lamivudine could replace emtricitabine to constrain costs. The evidence for their clinical equivalence with tenofovir-DF and NNRTIs in ART naive HIV-1 patients is inconclusive. The aim of this study was to evaluate the virological responses to lamivudine and emtricitabine in combination with tenofovir-DF and efavirenz or nevirapine in the ATHENA cohort.

Methods
Nationwide cohort study between 2002 and 2012 on 4740 ART naive HIV-1 infected patients without documented baseline resistance.

Six clinical endpoints
1. Week 48 virological failure.
2. Week 240 virological failure.
3. Time to virological failure within 240 weeks.
4. Time to 2 consecutive HIV-RNA <400 within 48 weeks.
5. Time to virological failure after HIV-RNA <400 within 240 weeks.
6. Acquired resistance to reverse transcriptase at virological failure.

Virological failure was defined by (1) any HIV-RNA >400 within 5810 weeks, (2) ART switch for documented failure, (3) death while last HIV-RNA >400. Virological responses were analyzed on-treatment by multivariate logistic regression analysis and Cox proportional hazard regression models. Sensitivity analysis included intent-to-treat models and propensity score analysis.

Baseline Characteristics

Results
Time to virological failure and time to various reasons for ART switches.

More virological failure with lamivudine than emtricitabine, regardless of NNRTI.

Sensitivity analyses gave comparable results.

Time to HIV-RNA <400 and time virological failure after HIV-RNA <400 Adjusted HRs (95%CI) on HIV-RNA <400 and virological failure after HIV-RNA <400 with lamivudine compared to emtricitabine were 1.0 (0.9-1.2) and 1.6 (0.9-2.8) with efavirenz, and 1.0 (0.8-1.2) and 1.5 (0.8-2.9) with nevirapine.

Acquired resistance in patients with baseline WT and HIV-RNA >1000 at failure

Conclusions
The use of lamivudine instead of emtricitabine in combination with tenofovir-DF and efavirenz or nevirapine for ART naive HIV-1 patients was associated with more virological failure. The evidence for their equivalent recommendation with tenofovir-DF in NRTI backbones as part of first-line cART is based on indirect comparisons of lamivudine/abacavir with emtricitabine/tenofovir-DF. Our observations warrant a direct randomized blinded comparison of lamivudine with emtricitabine in tenofovir-DF and NNRTI containing cART.
## Background

The number of people on treatment in the UK rises by 7-10% per year for several years. Over 100,000 people could be on antiretroviral treatment in the UK by 2019. Efforts to find and treat 20-25% undiagnosed patients will increase costs. New guidelines for earlier initiation of treatment or even "test and treat" will further increase costs. There is increasing pressure on the NHS to lower costs.

### Costs of HIV drugs in the UK

As shown in Table 1, drugs for HIV are sold in the UK at prices far higher than in low-income countries:

### Table 1: Prices of HIV drugs in UK versus low-income countries: £ Sterling per person-year

<table>
<thead>
<tr>
<th>Drug/price</th>
<th>NHS List</th>
<th>Low-income countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>£2880</td>
<td>£34</td>
</tr>
<tr>
<td>FTC</td>
<td>£1956</td>
<td>£22</td>
</tr>
<tr>
<td>Abacavine</td>
<td>£2136</td>
<td>£140</td>
</tr>
<tr>
<td>3TC</td>
<td>£1608</td>
<td>£18</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>£2400</td>
<td>£30</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>£2040</td>
<td>£23</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>£2400</td>
<td>£30</td>
</tr>
<tr>
<td>Darunavir</td>
<td>£3600</td>
<td>£450</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>£3636</td>
<td>£150</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>£5652</td>
<td>£422</td>
</tr>
</tbody>
</table>

If drugs are still on patent, pharmaceutical companies can negotiate these high prices with the NHS. After patent expiry, drugs can then be sold by generic companies as well, at much lower prices.

### Methods

In this analysis, the future costs of HIV treatment in the UK were calculated, using the following 7 assumptions:

1. 72,000 people are taking antiretroviral treatment in the UK in 2014, with a rise of 8% per year to >100,000 in 2019, in line with previous years.
2. Pharmaceutical companies sell drugs to NHS at a 28% discount from list price.
3. Home care delivery is used for 70% of patients.
4. Generics are 80% cheaper than discounted NHS prices (Table 2).
5. Immediately after patent expiry, people switch from branded to generic HIV drugs.
6. Generic HIV drugs are approved in these years:
   - 2024: TDF/FTC (Truvada)
   - 2021: ETR
   - 2019: ABC/3TC (Kivexa)

### Results

In sensitivity analyses, we found that larger savings would be possible if:

1. There is competition between generic suppliers – lowering generic prices further. There is the potential for generic prices to approach those from low-income countries, in the long-term (Table 1).
2. People currently taking patented nevirapine XR switched to the generic version. This was not included in base-case analysis, but could save an additional £5 million per year.
3. There was increased use of home delivery
4. There was a large-scale switch to Pill + 3TC as maintenance therapy. This switch is supported by results from 4 randomised 48 week studies, mainly in suppressed patients.
5. Dose optimisation: EFV, DRV/r, ATV/r. This could lead to additional reductions in costs, but regulatory approvals of the new doses would be needed

Conversely, smaller savings would be achieved if:

1. There was slower uptake of generic drugs. For example if generics were not available at time of patent expiry, or clinicians decided to continue prescribing patented versions.
2. There was a limited number of generic suppliers, so 80% reductions in price could not be achieved.

### Conclusions

1. If all people with HIV infection in the UK switched from patented to generic antiretrovirals as they become available, there is the potential to save in the region of £1.25 billion in NHS drug costs over the next 5 years (2015-2019).
2. This switch in treatment would involve the average treated person increasing their pill count from 2.3 to 3.5 pills per day.
3. This money could be used to fund other much needed HIV programmes, such as HIV prevention or the treatment of HIV/HCV co-infection.
4. The benefit of patented fixed dose combinations over available, there is the potential to save in the region of £1.25 billion in NHS drug costs over the next 5 years (2015-2019).

### Figure 1: Predicted annual NHS costs of antiretrovirals

<table>
<thead>
<tr>
<th>Year</th>
<th>Option 1 patented drugs</th>
<th>Option 2 generic drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>£2.41 billion</td>
<td>£1.61 billion</td>
</tr>
<tr>
<td>2016</td>
<td>£2.41 billion</td>
<td>£1.61 billion</td>
</tr>
<tr>
<td>2017</td>
<td>£2.41 billion</td>
<td>£1.61 billion</td>
</tr>
<tr>
<td>2018</td>
<td>£2.41 billion</td>
<td>£1.61 billion</td>
</tr>
<tr>
<td>2019</td>
<td>£2.41 billion</td>
<td>£1.61 billion</td>
</tr>
</tbody>
</table>

Potential total saving = £1.25 billion, over 5 years
Regional Differences in Self-Reported HIV Care and Management in the EuroSIDA Study

K Laut1, A Mocroft2, JV Lazarus3, P Reiss3, J Rockstroh4, I Karpov3, A Rakhamanova3, B Knysz3, S Moreno5, P Gargalianos6, JD Lundgren1, O Kirk1, for EuroSIDA in EuroCoord

1CHIP, Department of Infectious Diseases and Rheumatology, Section 2100, Rigshospitalet – University of Copenhagen; 2University College London, Department of Infectious Diseases and Population Health, London, United Kingdom; 3University of Amsterdam and Stichting HIV monitoring, Academic Medical Center, Amsterdam, Netherlands; 4University Hospital of Innsbruck, Department of Infectious Diseases, Minx, Belarus; 5Bofen Hospital of Infectious Diseases, Dept 21, St Petersburg, Russian Federation; 6Wroclaw University School of Medicine, Dept of Infectious Diseases, Wroclaw, Poland; 7Hospital Ramon y Cajal, Servicio Enfermedades Infecciosas, Madrid, Spain; 8Gennimatas Hospital, 1st Internal Medicine Dept Infectious Dis Unit, Athens, Greece

BACKGROUND

EuroSIDA has previously reported a poorer clinical prognosis for HIV positive individuals in Eastern Europe (EE) as compared with patients from other parts of Europe, not solely explained by differences in patient characteristics. We explored regional variability in self-reported HIV management at individual EuroSIDA clinics. The goal was to identify opportunities to improve the apparent inequalities in health.

METHODS

A survey on HIV management was conducted in early 2014 in all currently active EuroSIDA clinics. Responders in EE were compared with clinics in all other EuroSIDA regions combined (non-EE) (Figure 1). Characteristics were compared between regions using Fishers exact test.

RESULTS

- Half of the EE clinics indicated following WHO guidelines, whereas most non-EE clinics followed EACS guidelines (Figure 2).
- Significantly fewer EE clinics performed resistance testing before ART and upon treatment failure (Figure 2).
- The majority of clinics requested viral load and CD4 measurements at least every 6 months for patients on as well as off ART (Figure 2).
- The majority of EE clinics, and 25% of non-EE clinics, indicated deferral of ART initiation in asymptomatic individuals until CD4 ≤350 cells/mm³ (Table 1).
- There were no significant regional differences in screening haematology, liver or renal function, which the majority of clinics reported to do routinely.
- EE clinics screened less for cardiovascular disease (CVD), and only about half screened for tobacco use, alcohol consumption and drug use (Figure 3).
- Screening for cervical cancer and for anal cancer was low in both regions (Figure 3).

CONCLUSIONS

We found significant regional variability in self-reported HIV management across Europe, with less resistance testing, screening for CVD and substance use in EE. EE clinics indicated deferral of ART initiation for longer than non-EE clinics. Screening for cervical cancer screening was poor in both regions. Whether differences in HIV management are reflected in clinical outcomes deserves further investigation.

The EuroSIDA Study Group

Legends: 1K Laut, 2A Mocroft, 3JV Lazarus, 4P Reiss, 5J Rockstroh, 6I Karpov, 7A Rakhamanova, 8B Knysz, 9S Moreno, 10P Gargalianos, 11JD Lundgren, 12O Kirk.

Figure 1

Regional differences in guidelines, resistance testing and monitoring

Figure 2

Regional differences in deferral of ART initiation

Figure 3

Regional differences in routine screening

Download poster at: www.chip.dk

HIV Glasgow Drug Therapy 2014

Kamilla Grønborg Laut

CHIP, Department of Infectious Diseases and Rheumatology, Section 2100, Rigshospitalet – University of Copenhagen
Tel: +45 35455760
Download poster at: www.chip.dk
Major Challenges in Clinical Management of TB/HIV Coinfected Patients in Eastern Europe Compared with Western Europe and Latin America

AM W Efsen1, A Schultz2, FA Post3, A Pantelle4, HJ Fur rer6, R Miller4, MH Losso2, J Toibaro2, A Skr ahin6, JM Miro9, JA Cayla10, E Girard11, M Bruyand12, N Obel13, DN Podleka revera1, JD Lundgrena, A Mocroft2, O Kirk1

1CHI P, Department of Infectious Diseases and Rheumatology, Section 2100, Rigshospitalet – University of Copenhagen; 2University College London, London, UK; 3King's College Hospital, London, UK; 4TB hospital 2, St. Petersburg, Russia; 5Bern University Hospital and University of Bern, Bern, Switzerland; 6Thorntree Market Centre, London, UK; 7Hospital J.M. Ramos Mejia, Buenos Aires, Argentina; 8Republican Research and Practical Centre for Pulmonology and TB, Minsk, Belarus; 9Hospital Clinic – IDIBAPS., Barcelona, Spain; 10Public Health Agency of Barcelona, Barcelona, Spain; 11Ospedale S Spallanzani (Rome), Rome, Italy; 12Centre Inserm U897, Bonneux, France; 13Rigshospitalit iet, Copenhagen, Denmark;

A full list of the TB/HIV Study Group investigators can be found in the acknowledgement section.

BACKGROUND
Rates of both TB/HIV coinfection and multidrug-resistant (MDR) TB are increasing in Eastern Europe (EE). Data on the clinical management of TB/HIV coinfected patients are scarce.

AIMS
• To study the clinical characteristics of TB/HIV coinfected patients in Europe and Latin America (LA) at TB diagnosis.
• Identify factors associated with MDR-TB.
• Assess the activity of initial anti-TB treatment regimens given the results of drug-susceptibility tests (DSTs).

METHODS
Characteristics of patients were compared across regions. Risk factors for MDR-TB were identified in logistic regression models. Among patients with DST done within the first month of anti-TB therapy, we linked empirical anti-TB treatment regimens to the DST results and calculated the distribution of patients receiving 0, 1, 2, 3 and ≥ 4 active drugs in each region. If a specific DST result was not available for a given drug, the patient was assumed to be sensitive to this drug; sensitivity analyses restricted patients with complete resistance results (DST results available for all anti-TB drugs used in the empirical treatment regimen) were also performed.

RESULTS
• 1413 TB/HIV coinfected patients were enrolled from 62 clinics in 19 countries in EE, Western Europe (WE), Southern Europe (SE) and LA from 01/01/2011 to 31/12/2013. Significantly differences were observed between EE, WE, SE and LA; in EE, TB/HIV patients had poorer exposure to cART, less often a definite TB diagnosis (culture or PCR positive for M. Tuberculosis), and more often MDR-TB compared to other parts of Europe and LA (Table 1 and 2).

• A history of injecting drug use, prior anti-TB treatment and living in EE were independently associated with MDR-TB (Figure 1).

• For 585 patients with available DST, the empirical anti-TB treatment contained ≥3 active drugs in 66% of patients in EE compared with 90-96% of patients in other regions (Figure 2a). Had the patients received empirical therapy with standard therapy (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol (RHZE)), the corresponding proportions would not have changed substantially (Figure 2b).

• Large intraregional variations in levels of MDR-TB and use of empirical RHZ-based anti-TB treatment were observed especially in EE, where the proportion of MDR-TB cases ranged from 11 to 59% between countries, and the use of RHZ-based empirical anti-TB treatment ranged from 54% to 96%.

CONCLUSIONS
• Empirc anti-TB therapy in EE was suboptimal, with less than two-thirds of patients receiving three active drugs, and improved compliance with standard RHZE treatment does not seem to be the solution. Improved management of TB/HIV patients requires routine use of DST, empirical anti-TB therapy according to prevailing resistance patterns, and more widespread use of cART.
Large disparities in HIV treatment cascades between eight European and high income countries: analysis of break points.

Alice Raymond1, Andrew Hill2, Anton Pozniak3
1Imperial College London, Department of Public Health, London, United Kingdom; 2Liverpool University, Molecular and Clinical Pharmacology, Liverpool, United Kingdom; 3St Stephens AIDS Trust, Chelsea and Westminster Hospital, St Stephens Centre, London, United Kingdom

Background
Higher antiretroviral treatment coverage is associated with lower HIV transmission rates and HIV-related deaths at the country level [1]. Furthermore, patients on antiretroviral treatment with undetectable HIV RNA levels have a significantly lower risk of clinical disease progression and onward HIV transmission. This study aimed to estimate and compare the percentage of all HIV infected people who are diagnosed, linked to care, taking antiretroviral treatment, and have undetectable HIV RNA, in eight European or high-income countries: USA, United Kingdom, France, the Netherlands, Denmark, Australia, Canada (British Columbia) and Georgia. These results were compared with countries in Sub-Saharan Africa.

Methods
For each country, the number of people in five key stages of the HIV treatment cascade were collected: 1: HIV infected, 2: Known to be HIV positive, 3: Linked to care, 4: Taking antiretroviral treatment, 5: Having undetectable HIV RNA. Estimates were extracted from national reports [2,3,4], the UNAIDS database and UNAIDS Gap report [5], conference proceedings [6,10], and peer reviewed articles [7,8, 9]. The quality of the estimates and reporting methods were assessed individually for each country, with selection criteria such as availability of nationwide database and routinely collected data. Treatment cascades were constructed using estimates from 2010-2013.

Results
The percentage of all HIV-infected people with undetectable HIV RNA ranged from 20% in Georgia to 62% in Australia. Of the high-income countries, the USA had the lowest percentage of individuals with undetectable viral load (25%). This was also lower than the average of Sub-Saharan Africa countries (29%). The pattern of the cascades differed between countries: in the United States there was a fall from 66% to 33% between linkage to care and start of antiretroviral treatment. However in Georgia, the greatest loss in the treatment cascade was at diagnosis, with 48% of undiagnosed HIV-infected individuals.

Conclusions
➢ There are great disparities among European and high-income countries in the percentage of HIV-infected individuals with undetectable HIV RNA
➢ The treatment cascades show different key break points, suggesting differences in HIV care between countries.

References
Georgia: [10] Chikvarishvili et al., 2013. IAS 2013 Poster Exhibition

This research project was supported by a grant from the St Stephens AIDS Trust
Results 1

A total of 3,841 patients were included. Of these, 3,179 were females. Median age was 36 (IQR 31-42) years.

Mode of HIV transmission were heterosexual contacts in 38%, homosexual contacts in 32%, injection drug use in 24%.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male (N=1,662)</th>
<th>Female (N=2,179)</th>
<th>Total (N=3,841)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>39 (33-45)</td>
<td>36 (31-42)</td>
<td>38 (31-42)</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm³)</td>
<td>512 (392-628)</td>
<td>586 (514-698)</td>
<td>559 (436-698)</td>
</tr>
<tr>
<td>Median CD4 cell count at enrolment</td>
<td>200 (100-350)</td>
<td>351-500</td>
<td>501-750</td>
</tr>
<tr>
<td>ART naïve</td>
<td>12 (8.5%)</td>
<td>11 (5.2%)</td>
<td>12 (5.3%)</td>
</tr>
<tr>
<td>ART experienced</td>
<td>22 (13.5%)</td>
<td>30 (14%)</td>
<td>32 (8.3%)</td>
</tr>
<tr>
<td>ART experienced/naïve</td>
<td>16 (9.9%)</td>
<td>19 (8.8%)</td>
<td>19 (5.5%)</td>
</tr>
</tbody>
</table>
| CD4 cell count and the risk of infective and non-infective SNAE in HIV-infected persons seen for care in Italy

Results 2

Overall, 432 non-infect and 385 infective SNAE were included.

The most frequent non-infective SNAE were malignancies (n=222, 46%), followed by hepatitis (n=167, 17%) and cardiovascular (n=146, 16%), Figure 1.

The most frequent infective SNAE were pneumonia (n=239, 53%) and endocarditis (n=115), Figure 1.

Figure 1. Percentage of non-infect (left) and infective (right) serious AIDS adverse events observed in the study.

Results 3

<table>
<thead>
<tr>
<th>Number with non-infective SNAE (PYFU)</th>
<th>CD4 cell count (cells/mm³)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;750</td>
<td>350</td>
<td>0.64 (0.51, 0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>750-1000</td>
<td>1000</td>
<td>0.51 (0.41, 0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>1500</td>
<td>0.41 (0.32, 0.52)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Contact information: Giordano Madeddu - giordano.madeddu@uniss.it - University of Sassari, Italy

Backlog

CD4 cell count and the risk of infective and non-infective serious non AIDS events in HIV-infected persons seen for care in Italy

Methods

We included all HIV-infected persons enrolled in the Kiras Foundation Study cohort who had at least one follow-up visit.

SNAE were grouped in infective (pneumonia, sepsis, endocarditis and meningitis) and non-infective (malignancies, chronic kidney disease, cardiovascular events, hepatic events and pancreatitis) categories.

Incidence of these event groups were calculated overall and according to baseline and current CD4 cell count (as <200, 201-300, 301-500, 501-750, and >750 cells/mm³) as number of events divided by person years of follow up (PYFU).

Participants' follow-up accrued from the date of enrolment (baseline) to a diagnosis of SNAE or their last visit.

An event was defined the first time one of the considered SNAE occurred so that each person contributed a single event.

A Poisson regression model for each of the two endpoints was used.

A competing risk approach was used (e.g. mortality for a reason different from that under analysis and mortality were considered competing risk events). Thus, for example, in the analysis with non-infective SNAE as the endpoint, follow-up of a person who developed an infective SNAE was truncated at the date of his/her last clinical visit (administrative censoring).

Results

Higher current CD4 count was associated with reduced risk of both infective and non-infective SNAE in ART-naïve and in patients on ART (Table 4).

The association was less strong in the group who stopped ART (for non-infect SNAE the p-value for interaction between current CD4 and ART status is 0.0061).

Conversely we found a weaker association between baseline CD4 count and risk of non-infect SNAE in people treated with ART (p-value for interaction 0.0001), Table 4.

When CD4 was considered separately we found no association with ART count (data not shown).

Table 4. Rates of non-infective SNAE by current and baseline CD4 count and use of ART.

- CD4 cell count and the risk of infective and non-infective serious non AIDS events in HIV-infected persons seen for care in Italy

International Congress on Drug Therapy in HIV Infection. November 26, 2014 – Glasgow

Contact information: Giordano Madeddu - giordano.madeddu@uniss.it - University of Sassari, Italy

Background

CD4 cell count is the most used indicator of immune function in patients with HIV infection and is the strongest predictor of disease progression and survival.

Even in the ART era, serious non-AIDS events (SNAE) are frequent in HIV patients receiving ART.

Current CD4 count has been shown to be more strongly associated with infective compared to non-infective SNAE and unable to predict cardiovascular events.

Objective

We investigated the relationship between baseline and current CD4 count and the risk of both infective and non-infective SNAE in HIV infected persons according to current ART use.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the study population.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (%)</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Mean CD4 cell count (cells/mm³)</td>
</tr>
<tr>
<td>Mode of HIV transmission (%)</td>
</tr>
<tr>
<td>Heterosexual contacts</td>
</tr>
<tr>
<td>Intrahospital contacts</td>
</tr>
<tr>
<td>Deaths/withdrawals</td>
</tr>
<tr>
<td>Median age (years)</td>
</tr>
<tr>
<td>CD4 cell count at enrolment (cells/mm³)</td>
</tr>
<tr>
<td>ART naïve</td>
</tr>
<tr>
<td>ART experienced</td>
</tr>
<tr>
<td>ART experienced/naïve</td>
</tr>
</tbody>
</table>

Current CD4 count and the risk of infective and non-infective serious non AIDS events in HIV-infected persons seen for care in Italy

Table 2. Rates of infective SNAE by current and baseline CD4 count and use of ART.

- CD4 cell count and the risk of infective and non-infective serious non AIDS events in HIV-infected persons seen for care in Italy

Table 3. Rates of non-infective SNAE by current and baseline CD4 count and use of ART.

- CD4 cell count and the risk of infective and non-infective serious non AIDS events in HIV-infected persons seen for care in Italy

Table 4. Rates of non-infective SNAE by current and baseline CD4 count and use of ART.

- CD4 cell count and the risk of infective and non-infective serious non AIDS events in HIV-infected persons seen for care in Italy

Conclusions

In a larger cohort of HIV infected patients seen for care in Italy the majority of SNAE were of non-infective origin.

Furthermore, there is evidence that the association between CD4 count and risk of both endpoints is stronger in ART-naive compared to treated participants. In particular, for the risk of non-infective SNAE and when fitting the CD4 count as categorical, there was no evidence for a difference in the risk comparing different CD4 count strata, suggesting that baseline CD4 is a much less useful predictor for this endpoint. This emphasise the importance of achieving CD4 count recovery on ART to prevent these events.
Effects of age on symptom burden, mental health and quality of life amongst people with HIV in the UK

Ms Jennifer A McGowan1, Prof Lorraine Sherr1, Prof Martin Fisher2, Dr. Alison J Rodger1, Prof Margaret Johnson4, Prof Sarah Gilbert3, Prof Martin Fisher2, Dr. Alec Miners3, Prof Margaret Johnson4, Prof Jenifer A McGowan1, Prof Lorraine Sherr1, Dr. Alison J Rodger1, Prof Margaret Johnson4, Prof Sarah Gilbert3, Prof Martin Fisher2, Dr. Alec Miners3, Prof Margaret Johnson4, Prof Jenifer A McGowan1, Prof Lorraine Sherr1, Dr. Alison J Rodger1, Prof Margaret Johnson4, Prof Sarah Gilbert3, Prof Martin Fisher2, Dr. Alec Miners3, Prof Margaret Johnson4, NIAA and the Comprehensive Clinical Research Network. The views expressed in this presentation are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.


Acknowledgments:
were assessed; adjustment was made for gender/sexuality (MSM; het. Men, women), ethnicity.

1418 (49.3%) recruited from 8 UK clinics in 2011-12 (64% response rate) self-completing a questionnaire.

Table 2. Adjusted association of age and time with diagnosed HIV with prevalence of distressing symptoms, depression, anxiety and HrQoL problems

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall physical symptom distress (N=3042)</th>
<th>Overall HIVQoL (N=3042)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td>CR 95% C.I.</td>
<td>CR 95% C.I.</td>
</tr>
<tr>
<td>&lt;30</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>30-40</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>40-50</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>50-60</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>≥60</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Interaction</td>
<td>0.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>p-value</td>
<td>0.003</td>
<td>0.028</td>
</tr>
</tbody>
</table>

Table 1. Physical symptoms and symptom distress ordered in relation to prevalence of distress (most prevalent in bold).

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Present</th>
<th>Mildly Distressing</th>
<th>Distressing</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>3042</td>
<td>525 (17.2)</td>
<td>613 (21.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>762 (24.0%)</td>
<td>554 (17.0%)</td>
<td>268 (8.2%)</td>
</tr>
<tr>
<td>Headaches</td>
<td>890 (27.3%)</td>
<td>844 (27.6%)</td>
<td>6 (0.2%)</td>
</tr>
<tr>
<td>Changes in fat in face or body</td>
<td>920 (32.0%)</td>
<td>995 (34.5%)</td>
<td>213 (7.0%)</td>
</tr>
<tr>
<td>Muscle aches or joint pains</td>
<td>486 (15.9%)</td>
<td>417 (15.4%)</td>
<td>5 (0.2%)</td>
</tr>
<tr>
<td>Reduced appetite</td>
<td>407 (13.1%)</td>
<td>319 (10.7%)</td>
<td>3 (0.1%)</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>730 (24.0%)</td>
<td>688 (22.4%)</td>
<td>26 (0.8%)</td>
</tr>
<tr>
<td>Rash</td>
<td>1198 (41.4%)</td>
<td>1195 (41.3%)</td>
<td>2 (0.0%)</td>
</tr>
<tr>
<td>Itching</td>
<td>1137 (39.5%)</td>
<td>1136 (39.4%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Dryness</td>
<td>1115 (38.7%)</td>
<td>1114 (38.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1137 (39.5%)</td>
<td>1139 (39.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Increased problems in hands or feet</td>
<td>762 (24.0%)</td>
<td>762 (24.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Influenza</td>
<td>404 (12.4%)</td>
<td>522 (17.1%)</td>
<td>62 (2.0%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>404 (12.4%)</td>
<td>522 (17.1%)</td>
<td>62 (2.0%)</td>
</tr>
</tbody>
</table>

The mean age for participants was 45 years (SD=10, range 18-88 years). 168(5.5%) were under 30 years of age, 716(23.5%) between 30 and 40, 1301(42.8%) between 40 and 50, 657(21.6%) aged 50-60, and 220(7.2%) aged 60-70 years.

Conclusions
• Although physical and psychological symptoms are common among people living with HIV in the UK, the burden of these symptoms is not highest in the oldest age group.

Time diagnosed with HIV
Time diagnosed with HIV was significantly related to prevalence of overall physical symptom distress (table 2) and each symptom subgroup. Those diagnosed for longer were more likely to report distressing symptoms.

Longer time with diagnosed HIV was associated with higher prevalence of depression and anxiety symptoms and higher prevalence of HRQoL problems (table 2).

Background
The evolving HIV epidemic, coupled with advances in HIV treatment, has resulted in an ageing HIV-diagnosed population. The prevalence of physical and psychological symptoms of HIV may be greatest among older people. Few studies have examined the effect of older age on well-being for people with HIV.

Methods
The ASTRA study included 3258 HIV-diagnosed individuals (2048 MSM; 373 heterosexual men; 637 women) recruited from 8 UK clinics in 2011-12 (64% response rate) self-completing a questionnaire.

• Associations of age group with: physical symptom distress (reporting significant distress for ≥1 of 26 symptoms from an adjusted MSAS-BF scale), depression and anxiety (score ≥10 on PHQ-9 and GAD-7 respectively), and HRQoL problem (reporting problems on ≥1 of 5 EQ-5D-3L domains) were assessed; adjustment was made for gender/sexuality (MSM; het. Men, women), ethnicity (white; others) and time with diagnosed HIV (0-2; 2-10; 10+ years).

Figure 1. Prevalence of physical distressing symptoms (%) by age.

Age in Years

Figure 2. Prevalence of Depression, Anxiety and HRQoL (%) by age

Figure 3. Psychological Symptoms and HRQoL

Depression (PHQ-9 ≥10) was apparent in 871 (26.7%) of participants and anxiety (GAD-7 ≥10) in 715 (21.9%). The prevalence of symptoms of depression and anxiety decreased with age in unadjusted (fig. 2) and adjusted analysis (table 2). Prevalence of depression and anxiety symptoms increased with the number of present (p<0.0001) and distressing physical (p=0.0001) symptoms.

The prevalence of HRQoL problems was 63.3%. Overall, prevalence of HRQoL problems increased with age in unadjusted (table 2) and adjusted analysis. This increase was due to increased problems for 'mobility', 'self-care', 'pain' and 'performing usual activities' domains but not in 'depression/anxiety'.

Results
• Of all participants, 87% were taking ART, 76% had VLS<50/mL, 19% had CD4<350/mm³.
• The mean age for participants was 45 years (SD=10, range 18-88 years). 168(5.5%) were under 30 years of age, 716(23.5%) between 30 and 40, 1301(42.8%) between 40 and 50, 657(21.6%) aged 50-60 and 2006(6.6%) older than 60. 2220 (68.1%) of participants were Caucasian.

Physical Symptoms
• At least one symptom was reported as 'distressing' by 55.6%. The most prevalent distressing physical symptoms were: lack of energy/tiredness (26%), difficulty sleeping (24%), and muscle/ache/pain (21%). Although lower in prevalence, ‘pain’ and ‘changes in fat’ were most likely to cause distress when present (table 1, fig. 1).

• Using the overall physical symptom distress measure, after adjustment for gender/sexuality, ethnicity and time diagnosed with HIV, there was no overall trend with age (table 2).

Psychological Symptoms and HrQoL
• Depression (PHQ-9 ≥10) was apparent in 871 (26.7%) of participants and anxiety (GAD-7 ≥10) in 715 (21.9%). The prevalence of symptoms of depression and anxiety decreased with age in unadjusted (fig. 2) and adjusted analysis (table 2). Prevalence of depression and anxiety symptoms increased with the number of present (p<0.0001) and distressing physical (p=0.0001) symptoms.

• The prevalence of HRQoL problems was 63.3%. Overall, prevalence of HRQoL problems increased with age in unadjusted (table 2) and adjusted analysis. This increase was due to increased problems for ‘mobility’, ‘self-care’, ‘pain’ and ‘performing usual activities’ domains but not in ‘depression/anxiety’.

Conclusions
Although physical and psychological symptoms are common among people living with HIV in the UK, the burden of these symptoms is not highest in the oldest age group.

While HRQoL tended to worsen with older age amongst people with HIV, physical symptom distress did not, and mental health improved.

Longer time diagnosed with HIV was found to be strongly related to higher prevalence of all symptoms and decreased HRQoL. It may be a stronger factor than age in determining well-being.
Lack of Association Between Use of Efavirenz and Death from Suicide: D:A:D Study
C Smith1, L Ryom2, A d’Arminio Monforte3, P Reiss1, A Mocroft1, W el Sadr4, R Weber5, M Law7, C Sabin1, J Lundgren2
on behalf of the D:A:D Study Group

BACKGROUND
A recent meta-analysis performed by the ACTG of 4 RCTs in previously ART-naïve individuals showed a 2.28-fold increased rate of suicidality events among HIV-positive people receiving EFV compared to other, predominantly PI-based, regimens.4
There was also a trend towards an almost 3-fold higher rate of completed/attempted suicides, but the number of events was small (17 and 5 events)
We investigated whether the association between use of EFV and death from suicide observed in the clinical trial setting was replicated in an observational setting

METHODS
Participants were from the Data collection on Adverse events of anti-HIV Drugs (D:A:D) Study, a collaboration of 11 cohort studies in Europe, USA, and Australia
Consistent classification categories for causes of death was used across the study period following Coding of Causes of Death (CoDe) methodology
Individuals followed from D:A:D entry until death, 6 months after last clinic visit or 1st February 2013. Incidence rate ratios were calculated using Poisson regression
The primary outcome was defined in two ways as:
Suicide or psychiatric disease listed as underlying cause of death
Suicide or psychiatric disease listed as any of the underlying, immediate or contributing cause of death
We hypothesized that any psychiatric-related effects of EFV would appear upon initiation and
We investigated whether the association between use of EFV and death from suicide

RESULTS
There were 49,717 individuals participating in the D:A:D study (Table 1)
In 371,333 person-years of follow-up there were:
4,420 total deaths; rate=11.9/1000 person-years; (95% CI 11.6, 12.3)
193 deaths with underlying cause of suicide or psychiatric disease rate=0.52 (95% CI 0.45, 0.59)
482 deaths with suicide or psychiatric disease was mentioned anywhere on the death report; rate=1.30 (95% CI 1.18, 1.41)
There was a strong association between current CD4 and suicide-related deaths (Figure 1)
The highest rates of suicide deaths were seen amongst ART-experienced people currently on ART and ART-naïve individuals. For those on ART, similar suicide death rates were seen regardless of type of ART regimen (Figure 2)
After adjusting for potential confounders, similar associations remained (Table 3)
All sensitivity analyses provided consistent results

CONCLUSIONS
This study provides evidence that, amongst individuals in routine clinical care, rates of death from suicide and related causes for those receiving EFV-based ART are similar to those seen in individuals receiving other ART regimens
Treatment choices are at the clinician’s and patient’s discretion, and so it is possible and likely that the ART treatment groups are not comparable with respect to presence of underlying psychiatric and CNS-related disorders due to channelling bias. Unfortunately, information on history of psychiatric disease is not available
Thus these findings do not rule out the possibility that EFV leads to increased risk of suicide but they do provide re-assurance that the way in which the drug is used is not leading to increased suicide rates in those on the drug

1UCL, London, UK; 2CHiP, Department of Infectious Diseases and Rheumatology, Section 2100, Rigshospitalet – University of Copenhagen; 3San Paolo University Hospital, Milan, Italy; 4Academic Medical Center, University of Amsterdam, and Stichting HIV Monitoring, Netherlands; 5Mailman School of Public Health, Columbia University, New York, USA; 6University Hospital Zurich, University of Zurich, Zurich Switzerland; 7The Kirby Institute, University of New South Wales, Sydney, Australia

*All analyses were re-performed stratified by mode of HIV acquisition

**All analyses were re-performed restricted to those ART-naïve at baseline

### Table 1: Characteristics of D:A:D participants at Study Entry

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study population</th>
<th>Suicide or psychiatric disease (underlying cause)</th>
<th>Suicide or psychiatric disease (underlying, immediate or contributing cause)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>437,950 (48.0%)</td>
<td>239/50,985 (47.0%)</td>
<td>318/50,985 (62.6%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>214,258 (48.9%)</td>
<td>125/23,570 (53.7%)</td>
<td>230/23,570 (63.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>223,692 (51.1%)</td>
<td>114/27,415 (41.9%)</td>
<td>288/27,415 (53.4%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.0 (5.3)</td>
<td>59.2 (5.2)</td>
<td>58.2 (5.4)</td>
</tr>
<tr>
<td>CD4 cell count (cells/mm3)</td>
<td>500+</td>
<td>375/202,039 (61.0%)</td>
<td>545/202,039 (52.1%)</td>
</tr>
<tr>
<td>ART</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ART – naïve</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other ART</td>
<td>0.81 (0.49, 1.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other NNRTI-containing</td>
<td>0.73 (0.52, 1.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ART - experienced</td>
<td>2.71 (2.00, 3.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other NNRTI containing</td>
<td>0.67 (0.50, 0.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other ART – naïve</td>
<td>0.81 (0.49, 1.32)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other NNRTI-containing</td>
<td>0.73 (0.52, 1.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No ART - experienced</td>
<td>2.71 (2.00, 3.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other NNRTI containing</td>
<td>0.67 (0.50, 0.90)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Rates of death from suicide per 1,000 person years, according to current ART regimen

<table>
<thead>
<tr>
<th>ART</th>
<th>Rate per 1,000 person years (95% CI)</th>
<th>Rate per 1,000 person years (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART – naïve</td>
<td>1.02 (0.90, 1.15)</td>
<td>1.02 (0.90, 1.15)</td>
</tr>
<tr>
<td>Other ART</td>
<td>0.81 (0.49, 1.32)</td>
<td>0.81 (0.49, 1.32)</td>
</tr>
<tr>
<td>Other NNRTI-containing</td>
<td>0.73 (0.52, 1.03)</td>
<td>0.73 (0.52, 1.03)</td>
</tr>
<tr>
<td>No ART - experienced</td>
<td>2.71 (2.00, 3.67)</td>
<td>2.71 (2.00, 3.67)</td>
</tr>
<tr>
<td>Other NNRTI containing</td>
<td>0.67 (0.50, 0.90)</td>
<td>0.67 (0.50, 0.90)</td>
</tr>
</tbody>
</table>

**Table 3: Incidence Rate Ratios (IRRs) for death from suicide, according to current ART regimen

<table>
<thead>
<tr>
<th>ART</th>
<th>Unadjusted IRR (95% CI)</th>
<th>Adjusted IRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ART – naïve</td>
<td>1.00 (0.92, 1.08)</td>
<td>1.00 (0.92, 1.08)</td>
</tr>
<tr>
<td>Other ART</td>
<td>0.81 (0.49, 1.32)</td>
<td>0.81 (0.49, 1.32)</td>
</tr>
<tr>
<td>Other NNRTI-containing</td>
<td>0.73 (0.52, 1.03)</td>
<td>0.73 (0.52, 1.03)</td>
</tr>
</tbody>
</table>

Download poster at: www.chip.uk
A clinically useful risk-score for chronic kidney disease (CKD) in HIV infection

A Mocroft1, JD Lundgren2, M Ross3, M Law4, P Reiss5, O Kirk6, C Smith1, D Wentworth7, J Neuhaus8, CA Fux9, O Moranne9, P Morlat10, MA Johnson10, L Ryom10 on behalf of the Data on Adverse Events (D:A:D) study group, the Royal Free Hospital Clinic Cohort and the INSIGHT study group.

1University College London, London, UK; 2CHIP, Department of Infectious Diseases and Rheumatology, Section 2100, Rigshospitalet – University of Copenhagen; 3Mount Sinai School of Medicine, New York, USA; 4University of New South Wales, Sydney, Australia; 5University of Amsterdam, The Netherlands; 6University of Minnesota, Minneapolis, USA; 7Kantonsspital Aarau, Switzerland; 8Université Bordeaux Segala, Bordeaux, France; 9Public Health department, CHU Nice, France; 10Royal Free Hospital NHS Trust, London, UK

BACKGROUND

Development of a simple, widely applicable risk-score for CKD would allow comparisons of the risks/benefits of starting potentially nephrotoxic antiretrovirals (ARVs).

MATERIALS AND METHODS

18055 HIV+ persons from the Data on Adverse Drugs (D:A:D) study with ≥3 eGFRs ≥1/1/2004 were included. Persons with use of TDF, ATV/r, ATPIV, and other bPI before baseline (first eGFR <60 ml/min/1.73m2 after 1/1/2004) were excluded. CKD was defined as confirmed (>3 months apart) eGFR <60. Poisson regression was used to develop a score predicting low (<0.5 points), medium (1-4 points) and high (>5 points) risk of developing CKD. Increased incidence of CKD associated with starting ARVs was modelled by including ARVs as time-updated variables. The risk-score was externally validated on 2 independent cohorts.

RESULTS

- Characteristics of the included persons are shown in Table 1
- 641 persons developed CKD during 103278.5 PYFU (incidence 6.2/1000 PYFU, 95% CI 5.7–6.7)
- Older, intravenous drug use, HCV+ antibody status, lower baseline eGFR, female gender, lower CD4 nadir, hypertension, diabetes and cardiovascular disease predicted CKD and were included in the risk-score (Figure 1).
- There was good discrimination between those at low, medium and high risk and incidence of CKD (Figure 2) with good discrimination
- The risk-score was externally validated on 2603 persons from the Royal Free Hospital clinic cohort (94 events, incidence 5.1/1000 PYFU; 95% CI 4.1–6.1) and 2013 persons from the control arms of SMART/ESPRIT (32 events, incidence 3.8/1000 PYFU; 95% CI 2.5–5.1). External validation showed consistent CKD rates across the low, medium and high risk groups (Figure 2).
- NNTH at 5 years in persons starting ATV or LPV/r was 1395, 142 and 20 respectively among those with low, medium or high risk of CKD. NNTH were 603, 61 and 9 for those with a low, medium or high risk of CKD starting TDF, ATVPIV or bPI.

CONCLUSIONS

Traditional and HIV-related risk factors were predictive of CKD; all are routinely available, making the risk-score easy to incorporate into clinical practise and of direct relevance for clinical decision making. NNTH in persons starting potentially nephrotoxic ARVs at high risk of CKD were low, and alternative ARVs may be more appropriate.
Gender Differences in the Use of Cardiovascular Disease-related Interventions Among HIV-positive persons: D:A:D Study

C I Hatleberg, L Ryom, W El-Sadr, A Mocroft, P Reiss, S de Wit, F Dabis, C Pradier, A d’Arminio Monforte, M Rickenbach, M Law, J Lundgren and C Sabín on behalf of the D:A:D study group

BACKGROUND

- There have been substantial reductions in the incidence of myocardial infarction (MI) and improvements in post-MI survival in the general population. However, these improvements have tended to lag in women compared to men (1, 2).
- Reasons for this gender difference remain unclear but may possibly be explained by less use of drug interventions and invasive cardiovascular procedures (ICPs) in women (2,3).
- There is a lack of corresponding data related to potential gender differences in the use of interventions to prevent and treat cardiovascular disease (CVD) among HIV-positive individuals.

STUDY AIM

To investigate whether gender differences exist in the use of CVD-related interventions among HIV-positive participants in the D:A:D study.

METHODS

- The D:A:D Study is an observational study of >49,000 HIV-positive persons from 11 cohorts across Europe, Australia and USA. The primary aim of the study is to investigate potential associations between the use of antiretroviral drugs (ARVs) and CVD (MIs, strokes, ICPs) and other clinical events. Data are collected prospectively: the standardized dataset includes information on socio-demographic, HIV-and CVD-related factors.

STATISTICAL METHODS

- Follow-up was from 01/02/99 until the earliest of death, six months after last visit or 01/02/13.
- Individuals with a MI/stroke at baseline were excluded.
- Rates of initiation of lipid-lowering drugs (LLDs), angiotensin-converting enzyme inhibitors (ACEIs), anti-hypertensives and receipt of ICPs (bypass, angioplasty, endarterectomy) were calculated overall and in groups determined to be at higher CVD risk (i.e., periods of time in person years (PYRs)) where individuals were at higher CVD risk:
  - to total cholesterol (TC) >6.2 mmol/l
  - triglyceride (TG) >2.3 mmol/l
  - hypertension
  - previous MI
  - diabetes
  - age >50 years
  - 10-year Framingham CVD risk score >10%
- Poisson regression was used to assess whether rates of initiation of CVD-related interventions were higher in men than women, after adjustment for potential confounders.

RESULTS

- Baseline characteristics of men and women at enrolment in the D:A:D Study are shown in Table 1.
- Of 49,071 individuals without a MI/stroke at baseline, 0.6% women vs. 2.1% men experienced a MI while 0.8% women vs. 1.3% men experienced a stroke.
- The overall rates of initiation of LLDs, ACEIs, anti-hypertensives and ICPs were all lower in men than women (Figure 1).
- Rates of initiation of lipid-lowering drugs (LLDs), angiotensin-converting enzyme inhibitors (ACEIs), anti-hypertensives and receipt of ICPs (bypass, angioplasty, endarterectomy) were higher in men than women, after adjustment for potential confounders (Table 2).
- Additional adjustment for race, smoking status, AIDS, CVD family history and stroke as well as TC, TG, systolic/diastolic blood pressure as continuous covariates, had minimal effect on the observed associations with gender.

CONCLUSION

- The initiation rates of most CVD-related interventions, except for anti-hypertensives, were lower among HIV-positive women than men in the D:A:D study.
- Our findings suggest that actions should be taken to ensure that both men and women are monitored for CVD and, if eligible, receive appropriate CVD-related interventions.
- As women are most often found within low CVD risk groups, further investigation of the potential differences in monitoring of CVD risk factors between men and women are warranted as women may be less frequently and less sufficiently monitored.

REFERENCES:


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Camilla Ingrid Hatleberg

Poster No. 0324

HIV Glasgow Drug Therapy 2014

D:A:D

Gender Differences in the Use of Cardiovascular Disease-related Interventions Among HIV-positive persons: D:A:D Study

C I Hatleberg, L Ryom, W El-Sadr, A Mocroft, P Reiss, S de Wit, F Dabis, C Pradier, A d’Arminio Monforte, M Rickenbach, M Law, J Lundgren and C Sabín on behalf of the D:A:D study group

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REFERENCES:


Download poster at: www.chip.dk

Camilla Ingrid Hatleberg
Cenicriviroc (CVC) blocks HIV entry but does not lead to redistribution of HIV into extracellular space like maraviroc

Victor G. Kramer1, Said Hassounah1, Susan P. Colby-Germinario1, Thibault Mesplède1, Eric Lefebvre2, Mark A. Wainberg1
McGill AIDS Centre, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada; *Tobira Therapeutics, Inc., South San Francisco, CA, USA

Abstract 2916212

Ex vivo sub-analysis of Study 202

• Intracellular strong-stop HIV DNA (a marker of HIV entry) declines in Week 24 were pronounced in both CVC arms (CVC 100 mg: 51% decline; CVC 200 mg: 37% decline; Figure 2a).

• In contrast, no strong-stop declines were observed in the EFV arm (mean 1% increase).

• The differences between all three arms did not reach statistical significance.

• Full-length HIV DNA (a marker of late reverse transcription) declines were evident with CVC.

• The differences between all three arms were not statistically significant.

In vitro assays of PPM-1 cells

• Viral load for CVC-treated cells remained stable between baseline and 4 hours (0 hr: 1.9 x 10^10 copies/mL, 4 hrs: 3.6 x 10^9 copies/mL, Figure 3a), while MVC-treated cells exhibited a slight increase in viral load at 4 hours versus baseline (0 hr: 1.9 x 10^10 copies/mL, 4 hrs: 1.67 x 10^10 copies/mL).

• Four hours post-infection, CVC-treated cells showed lower levels of p24 compared with baseline (0 hrs: 536 ng/mL, 4 hrs: 172 ng/mL, Figure 4a); in contrast, p24 levels were similar at both time points for MVC-treated cells (0 hrs: 356 ng/mL, 4 hrs: 350 ng/mL).

• The relative intracellular strong-stop HIV DNA level was 0.1 in CVC-treated cells (compared with no-thought controls), which was significantly lower than the level of 0.33 in MVC-treated cells (p=0.02, Figure 4).

In silico assessment of CCR5 binding

• Docking simulations indicated that CVC binds only at the hydrophobic pocket in the CCR5 structure, which is also known as the ligand-binding pocket.

• Three CVC binding sites were identified (Figure 5): Sites 1 and 2 penetrate deep into the hydrophobic pocket and fill a large volume, while site 3 is in the entrance of the cavity.

• CVC and MVC occupy similar regions in the binding pocket of CCR5 (Figure 6); however, MVC occupies the middle of the binding pocket, while CVC is oriented to one side of the pocket and occupies a larger surface area.

• Some residues important for CCR5 binding may remain accessible in the presence of docked CVC, but not MVC.

Conclusions

• Ex vivo sub-analysis confirmed that CVC treatment blocks HIV cell entry pronounced strong-stop HIV DNA (a marker of HIV entry) declines were evident with CVC.

• In vitro sub-analysis showed that CVC does not repel viral load back into the extracellular space.

• CVC and MVC, despite having similar antiviral mechanisms, appear to differ in regards to the interactions between cell-free virus and CCR5.

• This study highlighted a number of functional differences between CVC and MVC, which may be due to the observed differential binding of CVC to CCR5, compared with that of MVC.

Acknowledgements

• The authors would like to thank Dr. Wainberg’s Laboratory team (Tobira Therapeutics, Inc.: Fabiana Finger, Veronica Zanchilli and Maureen Ohlmer, for technical assistance; the subjects who took part in Study 202 and their families; and the study investigators and their staff).

• Assistance was provided by Sandra Whitehead, Apharman Health Communications.

Author disclosures

• Victor G. Kramer is now an employee of AbbVie.

• Said Hassounah has no conflicts of interest.

• Susan P. Colby-Germinario has no conflicts of interest.

• Thibault Mesplède has no conflicts of interest.

• Eric Lefebvre is an employee of Tobira Therapeutics, Inc.

• Mark A. Wainberg has no conflicts of interest, through the research was supported by the Canadian Institutes of Health Research.

References


Abbreviations

• ARIA, AIDS Research and Reference Reagent Program

• CCR2, C-C chemokine receptor type 2

• CCR5, C-C chemokine receptor type 5

• CCRX, C-X chemokine receptor type 4

• CEF, cell entry inhibitor

• EFV, efavirenz

• ELISA, enzyme-linked immunosorbent assay

• FTC, emtricitabine

• HIV, human immunodeficiency virus

• MVC, maraviroc

• NRTI, nucleoside reverse transcriptase inhibitor

• NNRTI, non-nucleoside reverse transcriptase inhibitor

• PEP, per-epitope based mixed epitope

• qRT-PCR, quantitative polymerase chain reaction

• TAR, transmembrane receptor

• TLR, toll-like receptor

• TMD, transmembrane domain

This study has been accepted for publication in the journal of Antimicrobial Chemotherapy.

Poster presented at HIV Glasgow 2014; 6 December 2014. Glasgow. Further presentation of this poster omission will also be given at HIV Glasgow on Thursday 6 November, 11:00 during the session ‘New HIV drugs’.
Background

- Maraviroc is a suitable alternative for aviremic subjects developing ART toxicity or needing to avoid drug interactions, but its prescription requires prior tropism testing.
- It is unknown if proviral HIV-1 DNA genotypic tropism testing is reliable to guide MVC initiation in asymptomatic subjects.
- In a previous 36-week virological and immunological analysis of the PROTEST study, initiation of MVC plus 2 NRTIs in asymptomatic subjects based on genotypic tropism testing of proviral HIV-1 DNA was associated with low rates of virological failure.
- Here we present the third 48-week analysis of the study.

Methods

- Phase 4, prospective, single-arm clinical trial 24 HIV care centers in Spain (ID: NCT01378910).
- Tropism testing centrifuged in 3 centers (Becedas, H-San Cadio Galdames and H-Fundación Macario, Madrid), using a standardized protocol.
- Indication criteria: 
  - MDR: virological failure to one抗 virus.
  - NY VTF, H 200-2500, using ART during the previous 9 months.
  - No substantial virological response to the ART started.
  - PI/HV by proviral DNA genotypic tropism testing (defined as G2P FPR>10% in a singleton).
- Initiated MVC with 2 NRTIs and were followed for 48 weeks.
- Virological failure = 2 consecutive VL>5000 c/mL.
- Recent adherence = (N pills taken/N pills prescribed during the previous week)*100.

Results

- Subjects characteristics (n=74)
  - Median age 36 years (IQR 29,43), 74% men.
  - Median CD4+ counts (cells/µL) 616 (214,1000).
  - Median (IQR) viral load 28 (18,42) copies/mL.
  - Median (IQR) creatinine (µmol/L) 88 (54,146).
  - Median (IQR) total cholestoral (mmol/L) 4.6 (2,6,6,7).
  - Median (IQR) triglycerides (mmol/L) 1.1 (0.7,2).
  - Median (IQR) HDL cholesterol (mmol/L) 1.1 (0,9,1.3).
  - Median (IQR) AST (U/L) 28 (17,46).
  - Median (IQR) ALT (U/L) 17 (11,23).
  - Median (IQR) albumin (g/L) 39 (33,41).
  - Median (IQR) creatinine (µmol/L) 86 (57,144).
  - Median (IQR) CD4+ counts (cells/µL) 616 (214,1000).
- Subjects characteristics (n=74) compared with the previous week.
- Recent adherence (%) = (# pills taken/# pills prescribed during the previous week)*100.

Conclusions

- Initiation of MVC plus 2 NRTIs in asymptomatic subjects based on genotypic tropism testing of proviral HIV-1 DNA is associated with low rates of virological failure up to one year.
- Only 2 subject developed R5-X4 switch.
- All ARTs reached virological suppression in 2/5 continued TDF/FTC + MVC exposure.
- NF was associated with resistance in 2/5 subjects, in 1 of them, TAMs likely pre-dated MVC initiation.
- MVC initiation was associated with improvements in Total Cholesterol, Triglycerides, GGT and aspartate Aminotransferase.

Acknowledgements

The PROTEST Study Group

Acknowledgements

"The PROTEST Study Group


Contact information: Eva Poveda, Federico García & Roger Paredes.

"
EFAVIRENZ 400 mg DAILY REMAINS NON-INFERIOR TO 600 mg: 96 WEEK DATA FROM THE DOUBLE-BLIND, PLACEBO-CONTROLLED ENCORE1 STUDY

Dianne Carey1 for the ENCORE1 Study Group

1. The Kirby Institute, UNSW Australia

Introduction

ENCORE1 was a 96-week randomised, double-blind, placebo-controlled, non-inferiority trial with participants recruited at 38 clinical sites across Africa, Asia, Central and South America, Australia, and Europe. The 48-week primary analysis demonstrated Efavirenz 400 mg was non-inferior to 600 mg EFV when combined with TDF/FTC as initial HIV therapy over 96 weeks.

Aim

To examine the durability of efficacy and safety of reduced (400 mg) versus standard (600 mg) dose EFV combined with TDF/FTC as initial HIV therapy over 96 weeks.

Methods

Participants

Participants were recruited between August 2011 and March 2012. Eligibility included HIV-1 infection, age ≥18 years, ART-naive, CD4+ count ≥50 to <500 cells/μL, plasma HIV-1 RNA viral load (pVL) ≥1,000 copies/mL, and no history of prior protease inhibitors or NNRTI-based therapy. Exclusion criteria included co-morbidities which might affect participation, breastfeeding, and active tuberculosis. Participants were randomised to either 400 mg Efavirenz (EFV400) or 600 mg Efavirenz (EFV600). Adolescents aged 12-15 years were eligible if they were accompanied by a legal guardian who provided informed consent.

Interventions

At baseline, participants were randomised 1:1 to fixed-dose daily TDF/FTC 300/200 mg (Truvada®) plus either EFV 600 mg (3 x 200 mg) (EFV600) or EFV 400 mg (2 x 200 mg) + 1 matched placebo (EFV400).

Data analysis

Participants were followed through week 96. All participants were included in the intention-to-treat (ITT) population. EFV600 was non-inferior to EFV400 with p<0.05 for the lower limit of the 95% CI difference (EFV600 minus EFV400) for the primary endpoint—time to loss of virological suppression (pVL <200 copies/mL) at 96 weeks. The non-inferiority margin was fixed at 6% difference (±0.6% difference in proportion).

Baseline characteristics were balanced between treatment groups (Table 1).

Table 1. Baseline characteristics by treatment group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EFV 600 mg</th>
<th>EFV 400 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>116 (38.0)</td>
<td>116 (38.0)</td>
<td>232 (74.8)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>37.0</td>
<td>37.0</td>
<td>37.0</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>25.2</td>
<td>25.2</td>
<td>25.2</td>
</tr>
<tr>
<td>African</td>
<td>35.9</td>
<td>35.9</td>
<td>35.9</td>
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<tr>
<td>Asian</td>
<td>35.9</td>
<td>35.9</td>
<td>35.9</td>
</tr>
<tr>
<td>Caucasian</td>
<td>28.2</td>
<td>28.2</td>
<td>28.2</td>
</tr>
<tr>
<td>CDC category A, %</td>
<td>28.2</td>
<td>28.2</td>
<td>28.2</td>
</tr>
<tr>
<td>Median pVL, log10 c/mL (IQR)</td>
<td>4.75 (3.8)</td>
<td>4.73 (3.8)</td>
<td>4.74 (3.8)</td>
</tr>
<tr>
<td>pVL, c/mL (IQR)</td>
<td>200 (1,000)</td>
<td>200 (1,000)</td>
<td>200 (1,000)</td>
</tr>
<tr>
<td>Median CD4+ T-cells per mm3</td>
<td>800 (700, 1,000)</td>
<td>800 (700, 1,000)</td>
<td>800 (700, 1,000)</td>
</tr>
<tr>
<td>CD4+ T-cells ≥500 c/mL, %</td>
<td>28.2</td>
<td>28.2</td>
<td>28.2</td>
</tr>
<tr>
<td>≤100K</td>
<td>97.6</td>
<td>98.8</td>
<td>-1.1</td>
</tr>
<tr>
<td>&gt;100K</td>
<td>90.3</td>
<td>92.0</td>
<td>-1.6</td>
</tr>
<tr>
<td>100K</td>
<td>90.3</td>
<td>92.0</td>
<td>-1.6</td>
</tr>
<tr>
<td>geno typing success</td>
<td>273 (97)</td>
<td>272 (101)</td>
<td>273 (99)</td>
</tr>
<tr>
<td>median CD4+ T-cells at week 96, n (95% CI)</td>
<td>570 (49.7)</td>
<td>570 (49.7)</td>
<td>570 (49.7)</td>
</tr>
</tbody>
</table>

At week 96, the ITT analysis showed 90% of participants in EFV400 and 90.6% of EFV600 had a pVL<200 c/mL difference (-0.6%; 95% CI: -5.2 to 4.0) fulfilling criteria for non-inferiority (Figure 2). Similar results were seen in NCF & PP analyses consistent across screening pVL, strata & <50 copies/mL threshold (Figure 2).

Table 2. Adverse events

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>EFV 400 mg</th>
<th>EFV 600 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pts with AEs</td>
<td>287 (89.4)</td>
<td>276 (89.3)</td>
<td>563 (89.3)</td>
</tr>
<tr>
<td>No. pts with SAE</td>
<td>24 (7.5)</td>
<td>32 (10.4)</td>
<td>-2.9</td>
</tr>
<tr>
<td>No. pts with AEs related to EFV</td>
<td>16 (5.0)</td>
<td>23 (7.5)</td>
<td>-8.3</td>
</tr>
<tr>
<td>No. pts with AE due to EFV/EFV/EFV*</td>
<td>10 (3.1)</td>
<td>23 (7.5)</td>
<td>-6.4</td>
</tr>
</tbody>
</table>

Figure 1. Trial profile

Figure 2. Non-inferiority comparisons at week 96 by population & baseline HIV-RNA strata

Figure 3. Mean change from baseline to week 96 in plasma HIV-RNA

Figure 4. Mean change from baseline to week 96 in CD4+ T-cells

Figure 5. Baseline HIV reverse transcriptase resistance

Conclusions

- These results confirm the durable non-inferiority of EFV 400 mg to EFV 600 mg when combined with TDF/FTC as initial HIV therapy at 96 weeks.
- Lower EFV dose demonstrated fewer EFV-related AEs and a trend to less treatment-related discontinuations.
- These outcomes strongly support rapid transition through normative treatment guidelines to recommend routine use of reduced dose EFV.

Acknowledgements

The Kirby Institute, UNSW Australia. The Kirby Institute is affiliated with the Faculty of Medicine, UNSW Australia. In the Kirby Institute is affiliated with the Faculty of Medicine, UNSW Australia. The Kirby Institute is affiliated with the Faculty of Medicine, UNSW Australia.

Funding: We thank all study participants. Gilead Sciences Inc. donated study medication. This work is supported by the National Health and Medical Research Foundation of Australia. The Kirby Institute is affiliated with the Faculty of Medicine, UNSW Australia. In the Kirby Institute is affiliated with the Faculty of Medicine, UNSW Australia. The Kirby Institute is affiliated with the Faculty of Medicine, UNSW Australia. In the Kirby Institute is affiliated with the Faculty of Medicine, UNSW Australia.

References

Effectiveness of a reduced dose of efavirenz plus 2 NRTIs as maintenance antiretroviral therapy with the guidance of therapeutic drug monitoring

Shang-Ping Yang1, Wen-Chun Liu1, Kuan-Yeh Lee1, Bing-Ru Wu1, Yi-Ching Su1, Ya-Zhen Luo1, Hsin-Yun Sun1, Sui-Yuan Chang1, Shu-Wen Lin1, Chien-Ching Hung1
1National Taiwan University Hospital, Taipei, and 2National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu, Taiwan

Correspondence: Chien-Ching Hung
E-mail: hcc9605@ntu.edu.tw

Table 1. Clinical characteristics of the 157 patients switch to reduced dose of efavirenz-containing regimens

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%) or mean (interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (IQR), years</td>
<td>39 (31-45)</td>
</tr>
<tr>
<td>Male gender, %</td>
<td>94.3</td>
</tr>
<tr>
<td>Men who have sex with men, %</td>
<td>89.2</td>
</tr>
<tr>
<td>Weight, mean (IQR), kg</td>
<td>64 (56-71)</td>
</tr>
<tr>
<td>BMI, mean (IQR), kg/m²</td>
<td>22.1 (20.0-24.0)</td>
</tr>
<tr>
<td>Hepatitis B surface antigen (HBsAg) positive, %</td>
<td>25.8 (38/147)</td>
</tr>
<tr>
<td>Anti-HCV-positive, %</td>
<td>6.0 (9/151)</td>
</tr>
<tr>
<td>Duration of efavirenz exposure before switch, years</td>
<td>5.4 (1.45-9.07)</td>
</tr>
<tr>
<td>CD4 before switch, mean (IQR), cells/mm³</td>
<td>579 (403-706)</td>
</tr>
<tr>
<td>Plasma efavirenz concentrations (C12) before switch</td>
<td>3.43 (2.48-3.99)</td>
</tr>
<tr>
<td>Plasma efavirenz concentrations (C12) before switch</td>
<td>1.74 (1.34-2.09)</td>
</tr>
<tr>
<td>Decrease of C12 EFV after switch, mean (IQR), %</td>
<td>47.0 (38.3-55.1)</td>
</tr>
</tbody>
</table>

Patients and Methods

1. Study period: 1 April, 2013 to 31 October, 2014.
2. Study subjects: HIV-infected patients aged 20 years or older
   a. on stable therapy with efavirenz (600 mg) plus 2 NRTIs
   b. not concurrently taking rifampin or other medications with potential drug-drug interactions with efavirenz
   c. with plasma HIV RNA load <200 copies/ml after 6 months of longer therapy
3. Efavirenz was cut half by a cutter (Figure 1)
4. Plasma efavirenz concentration measured using HPLC 12 hours after taking the previous evening dose (C12 EFV) of >2.0 ng/ml.
5. Plasma HIV RNA load (PVL) determined by Roche real-time PCR (limit of detection, 20 copies/mL) and CD4 cell counts determined by flow cytometry; hematology and chemistry before switch, and weeks 4-12, 24, 36 and 48
6. Single-nucleotide polymorphism of CYP2B6 516GT was determined.
7. Primary endpoint: the proportion of subjects achieving PVL<50 copies/ml at 24 weeks after switch to reduced dose of efavirenz.

Results

1. During the 19-month study period, 157 HIV-infected patients were enrolled to switch to efavirenz at a dose of ½# (300-mg) efavirenz
2. The C12 EFV before and after switch are shown in Figures 2 and 3. The plasma C12 EFV decreased by a mean of 47.0% (interquartile range, 38.3-55.1%) 4 weeks after switch to the reduced dose of efavirenz.
3. The proportion of patients achieving PVL<50 copies/ml at weeks 24 and 48

Conclusions

We conclude that, with the guidance of therapeutic drug monitoring, a switch regimen containing efavirenz at a daily dose of 300 mg plus 2 NRTIs continues to achieve good viral suppression in the patients who have achieved prolonged viral suppression and C12 EFV >2.0 ng/ml with efavirenz at a full dose plus 2 NRTIs.
Week 48 efficacy analysis of the PROTEA trial: darunavir/ritonavir monotherapy versus darunavir/ritonavir with two nucleoside analogues, for patients with HIV-1 RNA below 50 copies/mL at baseline


Address for correspondence: Andrea Antinori, National Institute of Infectious Diseases, Rome, Italy  Email: andrea.antinori@inmi.it

Background

In the PROTEA trial, 273 patients with HIV-1 RNA suppression at baseline and no history of virological failure were randomised to receive darunavir/ritonavir (DRV/r) 800/100 mg once daily, either as monotherapy or in combination with two nucleoside analogues (N(t)RTI) for 96 weeks. The primary analysis was at Week 48.

Methods

Design: multicentre, randomised, open-label Phase 3b study to assess HIV-1 RNA suppression in patients receiving DRV/r monotherapy versus triple therapy containing DRV/r+N(t)RTIs

Primary outcome: proportion of patients in the intent-to-treat (ITT) population with confirmed virologic response (HIV-1 RNA <50 copies/mL) at Week 48, FDA Snapshot algorithm.

Inclusion: HIV-1 infected subjects, suppressed on first-line ARV regimen, CD4 nadir >100 cells/µL

Recruitment and randomization: approx. 260, randomised in a 1:1 ratio and stratified by HCV antibody results (anti HCV negative or positive)

Figure 1: Trial design

The trial was powered to show non-inferiority of the DRV/r arm versus the triple therapy arm (non-inferiority margin -12%). The primary endpoint was HIV-1 RNA suppression <50 copies/mL, at Week 48 using the FDA snapshot algorithm. In this analysis, any switch in treatment was classified as treatment failure.

In secondary analyses, the analysis was repeated for the subgroups of HCV antibody positive or negative, and CD4 nadir <200 cells/µL. In this post-hoc analysis, the difference in efficacy between the arms was large for the patients with CD4 nadir <200 cells/µL, but was not seen for the patients with higher CD4 nadir. This analysis was repeated for other cut-off levels for CD4 nadir, but the level of 200 cells/µL showed the strongest correlation with treatment failure.

Table 1 shows summary baseline characteristics by treatment arm. Patients were 83% male and 87% white, with mean age 42 years.

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DRV/r arm</th>
<th>DRV/r+2NRTIs arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CD4 count (cells/µL)</td>
<td>593 (221-1630)</td>
<td>623 (175-1025)</td>
</tr>
<tr>
<td>Nadir CD4 count (cells/µL)</td>
<td>253 (5-910)</td>
<td>289 (20-703)</td>
</tr>
<tr>
<td>CDC Disease stage C</td>
<td>3.6%</td>
<td>2.2%</td>
</tr>
<tr>
<td>HCV antibody positive</td>
<td>9%</td>
<td>10%</td>
</tr>
<tr>
<td>Duration of HIV-1 infection</td>
<td>8.1 years</td>
<td>7.2 years</td>
</tr>
<tr>
<td>Duration of prior ARV therapy</td>
<td>5.7 years</td>
<td>5.3 years</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA &lt;40 copies/mL</td>
<td>75.2%</td>
<td>80.9%</td>
</tr>
</tbody>
</table>

Results

In the primary efficacy analysis, there was a lower percentage of patients with HIV-1 RNA suppression in the DRV/r monotherapy arm (86.1%) versus the triple therapy arm (94.9%).

Figure 2. HIV-1 RNA <50 copies/mL at Week 48, FDA snapshot, switch=failure

Figure 3. HIV-1 RNA <50 copies/mL at Week 48, FDA snapshot, switch=failure, by nadir CD4 count

In a post-hoc analysis, this loss of efficacy was seen only in patients with CD4 nadir below 200 cells/µL. Most patients who had elevations in HIV-1 RNA showed re-suppression of HIV-1 RNA <50 copies/mL after re-intensification with NRTIs.

There were no trends for improved safety in the DRV/r arm versus the triple therapy arm.

Table 3 shows summary safety data to Week 48. The percentage of patients with adverse events was slightly higher in the PI monotherapy arm. There was no difference between the arms in the risk of psychiatric or nervous system adverse events.

Table 3. Treatment-emergent adverse events to Week 48

Conclusions

DRV/r monotherapy showed lower efficacy versus triple antiretroviral therapy at Week 48 in the primary switch equals failure analysis (86% versus 95%).

In a post-hoc analysis, this loss of efficacy was seen only in patients with CD4 nadir below 200 cells/µL. Most patients who had elevations in HIV-1 RNA showed re-suppression of HIV-1 RNA <50 copies/mL after re-intensification with NRTIs.

There were no trends for improved safety in the DRV/r monotherapy arm.

Based on review of the overall safety and efficacy results to Week 48, the Independent Data Monitoring Committee for the PROTEA trial recommended that all patients should be made aware of the 48 week results, and any patient with a CD4 nadir less than 200 cells/µL should be given the option to intensify from DRV/r monotherapy to triple combination treatment.

Acknowledgements: Thanks to all the patients, investigators and monitors who participated in the PROTEA study
Analysis of neurocognitive function and CNS endpoints in the PROTEA trial: darunavir/ritonavir with or without nucleoside analogues

1. Amanda Clarke, Brighton and Sussex Medical School, Brighton, United Kingdom 2. Veronika Johanssen, Karolinska University, Stockholm, Sweden 3. Jan Gerstoft, Copenhagen University Hospital, Copenhagen, Denmark 4. Clotet, Bonaventura University Hospital Germans Trias i Pujol, irsiCaixa, Badalona, Spain 5. Diego Ripamonti, University Hospital Bergamo, Italy

O423B

Background

In the PROTEA trial, 273 patients with HIV-1 RNA suppression at baseline and no history of virological failure were randomised to receive darunavir/ritonavir (DRV/r) 800/100 mg once daily, either as monotherapy or in combination with two nucleoside analogues for 96 weeks. The primary analysis was at Week 48.

The aim of this sub-study was to analyse changes in the neurocognitive test scores over time by treatment arm. In addition a subset of the PROTEA patients were enrolled in a study of HIV-1 RNA levels in the cerebrospinal fluid (CSF).

Methods

Design: multicentre, randomised, open-label Phase 3b study to assess HIV-1 RNA suppression in patients receiving DRV/r monotherapy versus triple therapy containing DRV/r (2NRTIs Primary outcome: proportion of patients in the intent-to-treat (ITT) population with confirmed virologic response (HIV-1 RNA <50 copies/mL) at Week 48

Inclusion: HIV-1 infected subjects, suppressed on first-line ARV regimen

Recruitment and randomization: approx. 260, randomised in a 1:1 ratio and stratified by HCV antibody results (anti HCV neg or positive).

Results

There was no difference between the arms in the percentage of patients who had at least one Grade 1-4 nervous system or psychiatric adverse event (Tables 2-3)

Table 2. Grade 1-4 nervous system adverse events to Week 48

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DRV/r arm</th>
<th>DRV/r+2NRTIs arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any nervous system AE</td>
<td>13 (9.5%)</td>
<td>14 (10.3%)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (5.6%)</td>
<td>6 (4.4%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>0</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Migraine</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Cognitive Disorder</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Mini-mental state</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>1 (0.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (1.5%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Paroxysmal behaviour</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
</tbody>
</table>

Table 3. Grade 1-4 psychiatric adverse events to Week 48

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DRV/r arm</th>
<th>DRV/r+2NRTIs arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any psychiatric AE</td>
<td>10 (7.3%)</td>
<td>9 (6.8%)</td>
</tr>
<tr>
<td>Depression</td>
<td>3 (2.2%)</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (2.2%)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2 (1.5%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Panic attack</td>
<td>0</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>Abnormal behaviour</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Lethargy</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Substance abuse</td>
<td>0</td>
<td>1 (0.7%)</td>
</tr>
</tbody>
</table>

Neurocognitive testing: global NPZ-5 score

There was no difference in neurocognitive performance between the treatment arms. There was a trend of general improvement in the scores over time in both treatment arms, which may be a learning effect.

Mean NPZ-5 score by treatment arm over time (95% C.I.)

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DRV/r arm</th>
<th>DRV/r+2NRTIs arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CD4 count cells/µL (median, range)</td>
<td>593 (221-1630)</td>
<td>623 (175-1025)</td>
</tr>
<tr>
<td>Nadir CD4 count cells/µL (median, range)</td>
<td>253 (5-910)</td>
<td>269 (20-703)</td>
</tr>
<tr>
<td>Nadir &lt;100 cells/µL</td>
<td>3.6%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Nadir 100-200 cells/µL</td>
<td>26.3%</td>
<td>19.9%</td>
</tr>
<tr>
<td>CDC Disease stage C</td>
<td>10.2%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Duration of HIV-1 infection 8.1 years</td>
<td>7.2 years</td>
<td></td>
</tr>
<tr>
<td>Duration of prior ARVs</td>
<td>5.7 years</td>
<td>5.3 years</td>
</tr>
</tbody>
</table>

HIV-1 RNA undetectable in CSF at baseline.

There were 40 patients with CSF samples taken both at baseline and Week 48. The CSF HIV-1 RNA results at Week 48 are shown for the 38 patients who were undetectable in CSF at baseline.

HIV-1 RNA in CSF samples at Week 48 for patients undetectable at baseline (<40 copies/mL – no detected)

Patient with treatment-emergent HIV-1 RNA in CSF

One additional patient in the DRV/r monotherapy arm, not in the CNS sub-study, was hospitalised with HIV encephalomyelitis at Week 24. This patient had a CD4 nadir of 17 cells/µL, which was below the inclusion limit of >100 cells/µL. At the baseline visit, the CD4 count was 430 cells/µL.

At Week 24, the HIV-1 RNA level in the CSF was 2500 copies/mL, with a plasma level of 500 copies/mL at the same visit. The patient was intensified with dolutivudine (300mg three times daily) and FTC (150mg twice daily), and the symptoms resolved.

At Week 48, the HIV-1 RNA was 45 copies/mL. At the most recent visit (Week 80), plasma HIV-1 RNA was <40 copies/mL?

Conclusions

There was no difference in neurocognitive performance between the treatment arms. There was a trend of general improvement in the scores over time in both treatment arms, which may be a learning effect.

However one patient in the PI monotherapy arm had HIV encephalitis at Week 24. A second patient had treatment-emergent HIV-1 RNA viraemia in CSF at Week 48. Both patients had low CD4 nadir <200 cells/µL.

Based on review of the overall safety and efficacy results to Week 48, the Independent Data Monitoring Committee for the PROTEA trial recommended that all patients should be made aware of the 48 week results, and any patient with a CD4 nadir less than 200 cells/µL should be given the option to intensify from DRV/r monotherapy to triple combination treatment.

Acknowledgements: Thanks to all the patients, investigators and monitors who participated in the PROTEA study.
Rate of viral load failure over time in people on ART in the UK Collaborative HIV Cohort (CHIC) study

Jemma O’Connor1, Colette Smith1, Fiona Lampe1, Margaret Johnson2, Caroline Sabin1, and Andrew Phillips1 on behalf of the UK Collaborative HIV Cohort (CHIC) Study. 1. University College London, UK 2. Royal Free Hampstead NHS Trust & UCL Medical School. Correspondence: jemma.oconnor@ucl.ac.uk

BACKGROUND

• Achieving and maintaining viral load (VL) suppression is central to the individual’s health and is also important for minimising transmission risk.

• Most people achieve and maintain VL suppression on first line antiretroviral therapy (ART).

• However, suppression is not achieved in all, and if achieved, may be followed by VL rebound at some future point.

• It remains uncertain whether those who have maintained long-term VL suppression will continue to do so over the long-term, or whether rates of VL failure will remain at appreciable levels.

• It therefore remains important to assess the propensity to experience VL failure after many years on ART.

AIMS

• To investigate the long term risk of VL failure in routine clinic patients and to determine factors associated with VL failure.

METHODS

• Participants were ART-naïve and started ART on or after 1st January 2000, with ≥3 drugs and at least 9 months of follow-up.

• Study Endpoints:
  - **Viral load failure (VF):** defined as failure to achieve VL suppression (<50 copies/mL) by 9 months after start of ART or a single VL >200 copies/mL 9 months after start of ART.
  - **Secondary endpoint: Viral load failure/interruption**
    - Take into account documented treatment interruption.
    - Interruption was defined as a record of being off ART for ≥ one month.

• For the primary endpoint (VF), participants were further required to have a VL measure in the period between 3 and 9 months after start of ART.

• Kaplan–Meier estimates were used to describe the cumulative probability of experiencing VL failure over time, irrespective of treatment interruption. Follow-up was censored at the last VL assessment but not at treatment interruption.

• Poisson regression was used to assess factors associated with the primary endpoint: viral load failure.

RESULTS

• 17,012 UK CHIC participants were included in the analyses. The characteristics of those included in the study are presented in Table 1.

• 6,029 (35.4%) participants experienced VL failure. Of these 6,029 participants, 1,857 failed to achieve suppression by 9 months after start of ART and the remaining 4,172 experienced a VL >200 copies/mL.

• Figure 1 presents the rates of VL failure per 100 person-years for both primary and secondary endpoints: viral load failure and viral load failure/interruption.

• Table 2 presents the results of a Poisson regression model fit to assess factors associated with VL failure.

DISCUSSION

• Rates of viral rebound continue to decline with extended periods on ART.

• However, first occurrence of VL >200 copies/mL continues to occur after having maintained viral suppression on ART for 10 years.

• It therefore remains important to consider the risk of VL rebound, even in people who have maintained VL suppression for 10 or more years.

Table 1: Baseline characteristics of participants included in analyses

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary endpoint: VF n=17,012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td>Female 4,850 (28.5)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td>White 8,911 (52.4)</td>
</tr>
<tr>
<td>Mode of HIV acquisition, n (%)</td>
<td>MSM 6,446 (49.7)</td>
</tr>
<tr>
<td>Regimen type, n (%)</td>
<td>NNRTI based 11,759 (69.1)</td>
</tr>
<tr>
<td>Age (median, Interquartile range [IQR])</td>
<td>37 [32-43]</td>
</tr>
<tr>
<td>Pre-ART HIV VL (copies/mL, median, [IQR])</td>
<td>73,600 [18,980-224,600]</td>
</tr>
<tr>
<td>Follow-up on ART (years, median, [IQR])</td>
<td>4.8 [2.8-7.7]</td>
</tr>
<tr>
<td>±10 years follow-up on ART n (%)</td>
<td>1,862 (11.0)</td>
</tr>
</tbody>
</table>

Table 2: Factors associated with viral load failure (VF)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Multivariable Relative Rate (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time on ART (years)</td>
<td>0.49 (0.48, 0.50)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age per 10 years</td>
<td>0.96 (0.93,0.99)</td>
<td>0.0030</td>
</tr>
<tr>
<td>Demographic group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black African heterosexual men</td>
<td>1.18 (1.09,1.29)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Black African heterosexual women</td>
<td>1.16 (1.01,1.34)</td>
<td></td>
</tr>
<tr>
<td>White heterosexual men</td>
<td>1.20 (1.13,1.29)</td>
<td></td>
</tr>
<tr>
<td>White heterosexual women</td>
<td>1.20 (1.04,1.38)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>1.13 (1.05,1.22)</td>
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<tr>
<td>Regimen type</td>
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<tr>
<td>PI based</td>
<td>1.38 (1.30,1.46)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Other</td>
<td>1.07 (0.95, 1.20)</td>
<td></td>
</tr>
<tr>
<td>NNRTI based</td>
<td>Reference</td>
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</tbody>
</table>
**HIV-1 Attachment Inhibitor Prodrug BMS-663068 in Antiretroviral-Experienced Subjects: Week 24 Subgroup Analysis**

**BACKGROUND**

BMS-663068 is a promising medication for the active management of ART-refractory patients. Its mechanism of action involves an inhibition of the attachment of HIV-1 to the cellular membrane, preventing viral entry and facilitating treatment of patients with HIV-1 who have failed standard ART.

**METHODS**

AI438011 study design

- Randomization: eligible subjects were randomly assigned to BMS-663068 or ATV/r arms.
- Efficacy: the primary endpoint was the proportion of subjects achieving an HIV-1 RNA <50 copies/mL at Week 24 regardless of age, gender, or race.
- Safety: adverse events were monitored throughout the study.

**RESULTS**

- **Subject disposition**:
  - 581 subjects were enrolled, 254 randomized and 251 treated.
  - 98% of patients achieved an HIV-1 RNA <50 copies/mL at Week 24.

- **HIV-1 RNA <50 copies/mL by gender, age or race**:
  - Mean increase in CD4+ T-cell count from baseline was similar across BMS-663068 and ATV/r arms irrespective of age or gender.

- **Mean change in CD4+ T-cell counts by gender, race or age**:
  - Similar increases in CD4+ T-cell count were seen in patients who described their race as ’Other’ (predominantly multiracial).

- **Summary**:
  - Virological response rates were similar across BMS-663068 and ATV/r arms throughout Week 24 regardless of age, gender, or race.

**ACKNOWLEDGEMENTS**

- The study was supported by Bristol-Myers Squibb, Princeton, NJ, USA.
- Professional medical writing and editorial assistance was provided by MedTech Media World Inc., Bridgewater, NJ, USA.

**REFERENCES**

BACKGROUND

Eligibility criteria

- Men or postmenopausal women of childbearing age
- Must be infected with HIV-1 for ≥18 weeks
- Must be on treatment for ≥4 weeks
- Must be treatment-naive
- Baseline CD4 count > 350 cells/μL
- Baseline HIV-1 RNA > 500 copies/mL
- Not pregnant or breastfeeding

Exclusion criteria

- Must not be pregnant or nursing
- Must not have a significant acute or chronic medical illness
- Must not have an active opportunistic infection
- Must not be treated with a study drug

RESULTS

BMS-663068 was generally well tolerated across all arms:

- Across the BMS-663068 arms, no noticeable trend for Grade 3–4 lab abnormalities
- Across the BMS-663068 arms, no dose relationship observed
- Across the BMS-663068 arms, no hemoglobin/platelet abnormalities
- Across the BMS-663068 arms, no viral resistance
- Across the BMS-663068 arms, no serious adverse events

SUMMARY

BMS-663068 was generally well tolerated across all arms.

OBJECTIVES

- To assess the safety and tolerability of BMS-663068 in combination with TDF + RAL with a background of RAL + TDF in up to 5 dose levels
- To assess the safety and tolerability of BMS-663068 in combination with TDF + RAL in up to 5 dose levels
- To assess the safety and tolerability of BMS-663068 in combination with TDF + RAL in up to 5 dose levels

METHODS

Phases Ia, I b, II, III, and IV:

- Phases Ia, I b, II, III, and IV: Intention-to-treat analysis
- Phases Ia, I b, II, III, and IV: Intention-to-treat analysis
- Phases Ia, I b, II, III, and IV: Intention-to-treat analysis

For the most study, subjects were randomly assigned to receive one of the following groups:

- Group 1: 300 mg/300 mg
- Group 2: 600 mg/600 mg
- Group 3: 1200 mg/1200 mg
- Group 4: 1800 mg/1800 mg
- Group 5: 2400 mg/2400 mg

Subject disposition

- 581 subjects enrolled, 254 randomised and 251 treated (Figure 4)
- 1 withdrew consent
- 1 no longer met inclusion criteria
- 3 lost to follow-up
- 1 adverse event
- Discontinued (n=8)

Table 4. Adverse events leading to discontinuation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BMS-663068 + TDF + RAL</th>
<th>ATV/r + TDF + RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events leading to discontinuation</td>
<td>1 (2.0%)</td>
<td>1 (2.0%)</td>
</tr>
</tbody>
</table>

Table 5. Adverse events leading to discontinuation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BMS-663068 + TDF + RAL</th>
<th>ATV/r + TDF + RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events leading to discontinuation</td>
<td>1 (2.0%)</td>
<td>1 (2.0%)</td>
</tr>
</tbody>
</table>

Table 7. Adverse events leading to discontinuation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BMS-663068 + TDF + RAL</th>
<th>ATV/r + TDF + RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events leading to discontinuation</td>
<td>1 (2.0%)</td>
<td>1 (2.0%)</td>
</tr>
</tbody>
</table>

Table 9. Adverse events leading to discontinuation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>BMS-663068 + TDF + RAL</th>
<th>ATV/r + TDF + RAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events leading to discontinuation</td>
<td>1 (2.0%)</td>
<td>1 (2.0%)</td>
</tr>
</tbody>
</table>
48-Week Efficacy and Safety and Early CNS Tolerability of Doravirine, a Novel NNRTI, With TDF/FTC in ART-Naive HIV-Infected Patients

Introduction

Doravirine (MK-1439): Novel NNRTI With Potential for Improved Efficacy and Safety

- Common NNRTIs associated with suboptimal efficacy and/or safety profiles:
  - Efavirenz—frequent CNS adverse events
  - Nevirapine—treatment-naive indication only for the US and EU
- High IC50 and broad spectrum of isolates
- Primary metabolite by CYP3A4; not an inducer or inhibitor
  - Once-daily dosing
  - Dosed without regard to food
- No interactions expected with proton pump inhibitors

Methods

PN007: Study Design

- Randomized, double-blind, 56-week, two-arm, dose-finding study
- Doravirine or efavirenz, both with TDF/FTC
- Dose groups assigned randomly until all patients complete final visit
- Population
  - Adults infected with HIV-1, extracellular treatments naive
  - HIV RNA >500 copies/mL, CD4 count <500 cells/µL
  - Stratified by HIV RNA >500,000 copies/mL or ≤500,000 copies/mL

- Part 1: 5-arm dose-ranging (N=200, 60 patients/group)
  - Doravirine 25, 100, 200, or 200 mg qd + TDF/FTC qd
  - Efavirenz + TDF/FTC qd
  - Dose selection based on Week 24 analysis

- Part 2: 2-arm (N=120 additional patients, 60 patients/group)
  - Allows powering of virologic response test for CNS AEs profile (Part 1 + 2 combined)
  - Doravirine 100 mg qd or efavirenz qd, both with TDF/FTC qd

PN007 Week 24 Analysis for Dose Selection

- Antiretroviral activity and immunological effect similar to efavirenz
- Good safety and tolerability profile
- Efavirenz >90% with HIV RNA <40 c/mL, <200 c/mL
- Dosed without regard to food

Results: Part 1, Week 48

- Efficacy endpoints
  - Virologic response rates: % with HIV RNA <40 c/mL, <200 c/mL
  - Baseline Characteristics
  - % Discontinued
  - CD4 (cells/µL), median (range)
  - % with HIV RNA >100,000 c/mL (screening)
  - Adverse event

- Primary Safety Comparison: CNS Events, All Causality
  - Hallucinations, dreams, nightmares, insomnia, suicidal ideation

- Resistance testing performed

- Patients with HIV RNA <200 c/mL (NC=F), % (95% CI)

Conclusions

In ART-naive, HIV-1-infected subjects:
- Doravirine 100 mg qd for 8 weeks demonstrates a significantly lower rate of treatment-emergent CNS events than efavirenz
- Doravirine 25-200 mg qd for 48 weeks also show:
  - Anti-HIV activity and immunologic effect similar to efavirenz
  - Low frequency of resistance development
  - Good safety and tolerability profile
- Week 48 data support continued development of doravirine 100 mg qd

Acknowledgments

The contributions of the investigators and their staff are likewise gratefully recognized.

References

3. A Baumgarten, D Schürmann, A Rall, R Moore, D Smith, D Cooper, 52nd ICAAC;2012.