XVIII International AIDS Conference 2010

Conference Review

Making Education Easy

18 – 23 July 2010, Vienna, Austria

In this issue:

Welcome

to our review of the XVIII International AIDS Conference, held recently in Vienna, Austria. The International AIDS Conference is the premier gathering for those working in the field of HIV, as well as policy makers, persons living with HIV and other individuals committed to ending the pandemic. The Conference programme presented new scientific knowledge and discussed the major issues facing the global response to HIV. Twelve of the most significant presentations have been independently selected and reviewed by Dr Rick Franklin, an Auckland-based specialist in sexual health, who attended this Conference.

We hope you find this Review interesting and helpful in your daily clinical practice.

Kind regards

Chris Tofield

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Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women

Authors: Karim QA et al

Summary: The CAPRISA 004 trial randomised 889 HIV-uninfected, sexually active South African women aged 18–40 years to receive 1% tenofovir vaginal gel (n=445) or placebo gel (n=444), to be used within 12 hours of intercourse, followed by a second application within 12 hours. HIV serostatus, safety, sexual behaviour and gel and condom use were assessed at monthly follow-up visits for 30 months. HIV incidence was nearly halved by tenofovir treatment, compared with placebo application, i.e. 5.6 per 100 women-years for tenofovir (person time of study observation, 38/680.6 women-years) compared to 9.1 per 100 women-years (60/660.7 women-years) in the placebo group (incidence rate ratio 0.61; p=0.017). Tenofovir gel reduced HIV acquisition by 54% in high adherers (gel adherence >80%), by 38% in intermediate adherers (50 to 80%) and by 28% in low adherers (<50%). Tenofovir was not associated with any increases in renal, hepatic, pregnancy-related or genital adverse events. There were no changes in viral load and no cases of tenofovir resistance in HIV seroconvertors.

Comment: The results of this trial were the highlight of the conference; once and for all establishing a 'proof of concept' for vaginal microbiocides. CAPRISA showed a modest preventative effect in this single trial involving heterosexual African women. Although this is a significant step in the prevention scenario, it is however just that, a step. In context, CAPRISA performed better than last year's Thai RV-144 HIV vaccine trial, but worse than three of the previous African circumcision trials. Although tenofovir vaginal gel appeared to have little toxicity or potential to create resistance, an overall effectiveness of 39% over 30 months will need to be considerably improved upon if microbiocides are to be successful.

Special Session: Safety and effectiveness of 1% tenofovir vaginal microbicide gel in South African women: results of the CAPRISA 004 trial. TUSS05

http://pag.aids2010.org/Session.aspx?s=13

Independent commentary by Dr Rick Franklin, Sexual Health Physician, Auckland District Health Board

Research Review publications are intended for New Zealand health professionals

HIV-1 elite controllers resist HIV-1 infection via p21 (cip-1/waf-1)

Authors: Chen H et al

Summary: These researchers analysed HIV-1 replication steps in CD4 T cells from elite controllers (n=15), HIV-1 negative individuals (n=14) and HIV-1 progressors (n=16) after *ex vivo* infection with a VSV-G pseudotyped HIV-1 vector or primary isolates. CD4 T cells from elite controllers were significantly less susceptible to HIV-1 infection compared to reference patient cohorts ($p<0.01$). This resistance was due to less effective reverse transcription and HIV-1 mRNA transcription from proviral DNA. RT-PCR and western blot analyses revealed that defective viral replication in CD4 T cells from elite controllers corresponded to significantly higher (by 10–20-fold) expression levels of p21 compared to those in the reference populations ($p<0.001$). In *ex vivo* infection assays, blockade of p21 significantly ($p=0.01$) enhanced reverse transcription and HIV-1 mRNA transcription in CD4 T cells.

Comment: Elite controllers (long-term nonprogressor [LTNP] patients) have always offered a potential window for new therapeutic directions. This study showed that changes found in LTNP patients, such as the difference in expression of p21, may offer a new way to alter host immunity.

Oral Abstract Session: Late Breaker Track A. THLBA101

http://pag.aids2010.org/Abstracts.aspx?AID=16896

TBR-652, a potent dual chemokine receptor 5/chemokine receptor 2 (CCR5/CCR2) antagonist in phase 2 development for treatment of HIV infection

Authors: Martin DE et al

Summary: Outcomes are reported from this dose-escalating investigation into the antiviral activity, safety, and tolerability of TBR-652, a potent dual chemokine receptor 5/chemokine receptor 2 (CCR5/CCR2) antagonist. A total of 54 HIV-1-infected, antiretroviral treatment-experienced, CCR5 antagonist-naïve, CCR5-positive patients were randomised to receive 25 mg, 50 mg, 75 mg, 100 mg, or 150 mg TBR-652 monotherapy or placebo orally once daily for 10 days. TBR-652 showed potent antiviral activity and a significant effect on HIV-1 RNA levels; median changes from baseline in HIV-1 RNA as assessed on Day 11 were –0.1, –0.5, –1.3, –1.6, –1.2, and –1.5 $\log^{10}$ copies/mL, respectively, for the placebo and 25 mg, 50 mg, 75 mg, 100 mg and 150 mg TBR-652 dosage groups. TBR-652 also had a significant effect upon monocyte chemoattractant protein (MCP)-1 expression; median changes from baseline in MCP-1 levels at Day 11 were 0, 25.0, 56.0, 36.0, 74.5, and 322.0 pg/mL, for the placebo and 25 mg, 50 mg, 75 mg, 100 mg and 150 mg TBR-652 dosage groups, respectively. TBR-652 monotherapy was generally well tolerated for 10 days at all dose levels, with predominantly grade 1 AEs, no serious AEs, no deaths, and only 1 discontinuation during dosing (not related to study drug).

Comment: AIDS XVIII had little in the way of new drugs at the end of the development pipeline. Therefore, this study, looking at a novel CCR5/CCR2 antagonist at the start of a development process, was interesting. The marked antiviral action of TBR-652 will make it worth keeping a watching brief on as it progresses to Phase 2 and beyond.

Oral Abstract Session: Antiretroviral Therapy: New Drugs and Novel Strategies. MOAB0104

http://pag.aids2010.org/Abstracts.aspx?AID=8023

Once-daily S/GSK1349572 as part of combination therapy in antiretroviral naïve adults: rapid and potent antiviral responses in the interim 16-week analysis from SPRING-1 (ING112276)

Authors: Arribas J et al

Summary: This Phase 2b study (SPRING-1) examined the antiviral activity of the novel next-generation HIV-1 integrase inhibitor, S/GSK1349572, in 205 therapy-naïve adults with HIV-1 infection, who were randomised to receive 10 mg, 25 mg or 50 mg of S/GSK1349572 or efavirenz (EFV) 600 mg once daily with either co-formulated tenofovir DF/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC). A planned Week 16 interim analysis revealed rapid decreases in plasma HIV-1 RNA across all S/GSK1349572 doses with no differences in gender or NRTI subgroups. Time to HIV RNA <50 copies/mL was shorter in S/GSK13249572 arms than the EFV arm (each $p<0.001$ vs EFV); by Week 4, 66% of S/GSK1349572 subjects were suppressed vs 18% on EFV. Two protocol-defined virological failures occurred; one EFV (<1 $\log_{10}$ decline by Week 4), and one S/GSK1349572 (Week 4 rebound with only M184V mutation detected). Most S/GSK1349572-related AEs were grade 1. More drug-related AEs of moderate-or-higher intensity were reported on EFV (18%) than S/GSK1349572 (6%) arms; none occurred in more than one S/GSK1349572 recipient. No SAE was considered related to S/GSK1349572. Five AE-related withdrawals occurred (1:S/GSK1349572 and 4:EFV). Mean change from baseline in LDL cholesterol was lower amongst S/GSK1349572 recipients (+0.066 mmol/L) than EFV recipients (+0.436 mmol/L).

Comment: The ODIS trial is undecided about once-daily raltegravir, so this study of a potent once-daily novel integrase inhibitor versus efavirenz on a standard ARV background is early but encouraging.

Oral Abstract Session: Late Breaker Track B – 2. THLBB205

http://pag.aids2010.org/Abstracts.aspx?AID=17600

Simplification from protease inhibitors to once or twice daily raltegravir: the ODIS trial

Authors: Vispo E et al

Summary: Outcomes are reported from one clinic where all HIV-infected patients on protease inhibitor (PI)-based regimens with plasma HIV RNA <50 copies/mL lasting >24 weeks were switched from PIs to raltegravir. Patients were randomly assigned to raltegravir 800 mg once daily, 400 mg twice daily, or twice daily for the first 3 months and then once daily. A total of 222 patients completed 24 weeks on raltegravir (149 once daily, 35 twice daily, and 38 twice daily to once daily arm). The most frequently replaced PIs were atazanavir (48%), lopinavir (28%) and fosamprenavir (13%). Raltegravir was given with tenofovir/emtricitabine to 69% of patients and with abacavir/lamivudine to 31%. Baseline mean CD4 count was 574 cells/µL and 46% were HCV-coinfected. Within 24 weeks, 13 (5.9%) patients experienced virological failure, 12 (6.4%) in the once-daily and 1 (2.9%) in the twice-daily arm ($p=0.18$). Virological failure rates were 16.2% (12/74) in patients with prior NRTI resistance versus 0.7% (1/148) in the remaining patients ($p<0.001$). Significant reductions in total, LDL and HDL cholesterol were observed at 24 weeks after switching to raltegravir.

Comment: This trial looked at switching fully suppressed patients from a PI to raltegravir at either the standard twice-daily dose, or a once-daily dose. This seemed to be a valid option, although more study information is needed before I could recommend raltegravir once daily.

Oral Abstract Session: Antiretroviral Therapy: New Drugs and Novel Strategies. MOAB0102

http://pag.aids2010.org/Abstracts.aspx?AID=12476

Triple class virologic failure in HIV-infected children

Authors: Butler K et al

Summary: The Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group assessed the medical records of 1007 perinatally HIV-infected children aged <16 years, who started ART with ≥3 drugs between 1998 and 2008. Virological failure of a drug was defined by a viral load >500 copies/mL despite 4 months of continuous use; triple-class virological failure (TCVF) was defined as virological failure of two NRTIs, an NNRTI, and a ritonavir-boosted PI (PI/r). The incidence of TCVF increased with time on ART; by 5 years after starting ART an estimated 7.3% of children had TCVF, higher than in adults in COHERE (HR 1.6; p<0.001). Multivariate analysis identified older age at ART initiation and previous AIDS diagnosis as factors associated with an increased risk of TCVF (p=0.005 and 0.02 respectively). NRTI, NNRTI and PI/r mutations were detected in 72% (26/36), 97% (28/29) and (0%) (0/15), respectively, of those with a resistance test while taking a drug of the corresponding class.

Comment: This study highlights issues faced by paediatricians treating HIV-infected children, and eventually as they move from adolescence to adult teams. The figure of 7% for TCVF may seem low, but it is not negligible, and does not appear to diminish over time from starting ART. If this trend continues, many patients are likely to need newer drugs to maintain viral suppression.

Oral Abstract Session: Treatment of Children: HIV in Children, Prognosis and Outcomes of Treatment. MOAB0204

http://pag.aids2010.org/Abstracts.aspx?AID=12551

Lack of regression of anal squamous intraepithelial lesions and anal HPV infection despite immune restoration under cART

Authors: Piketty C et al

Summary: The impact of cART on the natural history of HPV infection and anal squamous intraepithelial lesions (ASIL) was examined in 94 HIV-infected men who have sex with men (MSM), who enrolled in this study before starting a first-line regimen of cART. The median CD4 cell count increased from 299 cells/mm^3 at baseline to 500 cells/mm^3 at month 12; plasma HIV RNA levels decreased from a median of 4.8 to 1.6 log^{10} copies/mL. Prevalences of HPV infection, low- and high-grade SIL, were similar at baseline and month 12. Among patients with normal anal cytology and/or histology at baseline, 44% progressed to ASIL at month 12, whereas 31% of patients with ASIL at baseline had regressed by month 12. Specific anti-HPV CD4 T cell responses were mostly undetectable both at baseline and month 12.

Comment: This small French study suggests that there is a high rate of anal SIL in HIV-positive men, even in the face of good viral suppression and well maintained CD4 counts. This is perhaps not surprising, given what we currently know about perianal HPV. What is needed is a consensus on the best monitoring practice for anal SIL in HIV+ (and negative) MSM.

Oral Abstract Session: Malignancies in PLHIV. WEAB0103

http://pag.aids2010.org/Abstracts.aspx?AID=11857

Nadir CD4 is a predictor of HIV neurocognitive impairment (NCI) in the era of combination antiretroviral therapy (cART): results from the CHARTER study

Authors: Ellis R et al

Summary: These researchers examined the relationship between probability of neurocognitive impairment (NCI) and nadir CD4 counts, by exploring factors that may be related to both NCI and nadir CD4 in 1525 HIV-infected patients who were on or off cART. Unadjusted, lower nadir CD4 counts were strongly associated with NCI (p=0.004). This relationship remained significant in a logistic regression analysis that adjusted for nearly all demographic and disease-related covariates. After adjusting for cART use, however, nadir CD4 was no longer statistically significant. Since those taking cART had lower nadir CD4 counts than those not taking cART (146 vs 343 cells/μL; p<0.0001), analyses were repeated in the 589 patients on cART with an undetectable viral load in plasma. In this subgroup, nadir CD4 count remained a significant correlate of NCI after adjusting for age, comorbidity, and duration of infection (all p<0.05). Results were similar when examining only those with the fewest comorbidities.

Comment: This study continues the interest in neurocognitive impairment in those infected with HIV. The findings of increased rates of NCI with lower nadir CD4s emphasises the need for early identification of infection and earlier treatment than in the past.

Oral Abstract Session: Late Breaker Track B – 1. THLBB109

http://pag.aids2010.org/Abstracts.aspx?AID=17612

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Willingness to use, prescribe, or publicly fund PrEP services: results from 3 national surveys in the United States

Authors: Smith DK et al

Summary: Results are presented of multivariate analyses assessing correlates of willingness to use, prescribe, or publicly fund HIV pre-exposure prophylaxis (PrEP) with daily use of oral antiretrovirals. The data for these analyses were obtained from 3 national surveys: the DocStyles web survey (n=2150), the ConsumerStyles mail survey (n=10,958), and the HealthStyles mail survey (n=4556), conducted in the US in 2009. The surveys contained questions about HIV testing, PrEP knowledge and attitudes. While <4% of consumers reported having a high or medium chance of getting HIV infection, 42% would want to use PrEP. While 81% would recommend that friends or family members at high risk have access to PrEP, only 15% reported knowing something believed to be uninfected but at high risk. As many as 88% of clinicians indicated they would prescribe PrEP to at least one risk population.

Comment: See below

Abstract Session: CDC0621

http://pag.aids2010.org/Abstracts.aspx?AID=10089

Oral PrEP during mucosal SHIV infection reduces viremia, preserves CD4 counts, and raises potent T cell responses

Author: Kersh E et al

Summary: These researchers examined whether HIV pre-exposure prophylaxis (PrEP) with antiretrovirals has beneficial effects even when infection is not prevented. T cell responses were analysed in 11 rhesus macaques infected during up to 14 once-weekly, rectal, low-dose $SHIV_{SF162P3}$ exposures while receiving concurrent, oral Truvada (n=2), the novel tenofovir prodrug GS7430 (n=4), or no PrEP (controls; n=5). Drugs were continued for up to 20 weeks after infection. SHIV infection during PrEP resulted in lower peak viraemia compared to controls (median $\log^{10}$ = 5.5 or 7.5 copies/mL, respectively; p=0.02). PrEP-treated macaques had higher blood CD4 counts than controls (mean 257,000 and 86,000 cells/mL, respectively, p=0.0067) and higher T cell counts (p=0.0138) at peak viraemia; more SHIV-specific T cells simultaneously produced four cytokines (p=0.0001), and they recognised more SHIV-derived peptide pools (p=0.0366). When $CD8^+$ cells were deleted *in vivo* after PrEP, viraemia rose to similar levels in PrEP-treated macaques and controls, indicating that $CD8^+$ cells were critical for viral control.

Comment: See below

Bridging Session: Understanding HIV Transmission Mechanisms: Microbicides and PrEP. THBS03

http://pag.aids2010.org/Abstracts.aspx?SID=682&AID=2735

Exposure of extracellular and intracellular tenofovir and emtricitabine in mucosal tissues after a single of fixed-dose TDF/FTC: implications for pre-exposure HIV prophylaxis (PrEP)

Authors: Patterson K et al

Summary: Single-dose pharmacokinetics were evaluated in vulnerable mucosa in 8 HIV-negative men and 7 women after one tenofovir disoproxil fumarate/emtricitabine dose. Baseline characteristics were: age 19–37 years and 18.8–28.6 kg/m^2; 11 patients were white. Tenofovir could be detected post-dose for 14 days in blood plasma, vaginal tissue, and rectal tissue; for 7 days in cervical tissue. Intracellular tenofovir diphosphate concentrations were detected in all matrices for 14 days. Emtricitabine could be detected for 14 days in blood plasma and rectal tissue; for 10 days in vaginal tissue and cervical tissue. Intracellular concentrations of emtricitabine triphosphate could be detected for 10 days in peripheral blood mononuclear cells, for 2 days in vaginal tissue and rectal tissue, and for 1 day in cervical tissue.

Comment: See below

Bridging Session: Understanding HIV Transmission Mechanisms: Microbicides and PrEP. THBS0303

http://pag.aids2010.org/Abstracts.aspx?AID=16370

Looking beyond TDF based PrEP: criteria for identifying the next PrEP candidates

Authors: Fisher K et al

Summary: This research group notes that results of 3 clinical trials (CDC4323, CAPRISA004 and iPrEx) using antiretrovirals as pre-exposure prophylaxis (PrEP) are expected in 2010. The current oral PrEP pipeline relies on drugs that are recommended for first-line therapy in HIV; oral and topical TDF (tenofovir disoproxil fumarate) in MSM and heterosexual women and oral TDF/FTC (TDF/emtricitabine) in MSM. Relying heavily on only these two drugs raises concerns regarding resistance; other oral PrEPagents besides TDF and TDF/FTC will need to be considered. Researchers, product developers, implementers, advocates, and regulators were approached by AVAC to articulate the attributes of an optimal PrEP drug, to compare TDF and TDF/FTC to other potential next-generation PrEP agents, consider long term issues, and make decisions about the most appropriate way forward. The consensus was that optimal PrEP drugs would have high protection against HIV, a high barrier to resistance, acceptability to users, long-lasting activity, long-term safety data, and would not be part of any treatment regimen. This paper calls for multidisciplinary HIV prevention research stakeholders to team up with treatment advocates and providers to plan the next steps, following the release of data from the CDC4323, CAPRISA004 and iPrEx trials.

Comment: PrEP, or the use of preventative antiretroviral medication, is being studied in at-risk populations around the world, including MSM, IDUs and heterosexual populations in southern Africa. According to the poster shown at the CDC0621 session, awareness of the concept of PrEP is low. If trials like iPrEx show good results for prevention, then PrEP education and promotion will be of great importance.

AVAC: Global Advocacy for HIV Prevention. MOPE0373

http://pag.aids2010.org/Abstracts.aspx?AID=7488

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