HIV/AIDS Research Review™

Making Education Easy

Issue 12 - 2015

In this issue:

Abbreviations used in this issue:

AIDS = acquired immunodeficiency syndrome; **ART** = antiretroviral therapy; **AUC** = area-under-the-concentration-time curve; **BMD** = bone mineral density; **DHHS** = Department of Health and Human Services; **DXA** = dual energy x-ray absorptiometry; **FTC** = emtricitabine; **HIV** = human immunodeficiency virus; **HR** = hazard ratio; **IFN** = interferon; **NMT** = nontuberculous mycobacterial disease **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NRTI** = nucleoside reverse transcriptase inhibitor; **OR** = odds ratio; **PBS** = Pharmaceutical Benefits Scheme; **PLHIV** = People Living with HIV; **PrEP** = pre-exposure prophylaxis; **TDF** = tenofovir disoproxil fumarate;

Follow **RESEARCH REVIEW** Australia on Twitter now

@ResearchRevAus

Visit https://twitter.com/ResearchRevAus

Welcome to the twelfth issue of HIV/AIDS Research Review.

We begin this issue with a study investigating the long-term safety of polyacrylamide gel for facial lipoatrophy, and discover the agent to be associated with high patient satisfaction levels and few significant side effects. Following on, we discover that once-daily etravirine in combination with tenofovir disoproxil fumarate/emtricitabine for treatment-naïve HIV infected adults is also safe and effective. Other studies included in this issue look at bone mineral density and the risk of incident fracture, the long-term effects of raltegravir-containing regimens, regimen selection for HIV salvage therapy, disparities in combination ART initiation and virus suppression, darunavir pharmacokinetics in pregnant HIV-infected women, immune correlates of HIV-1 pre-exposure prophylaxis, long-acting intramuscular rilpivirine and trends in the incidence of nontuberculous mycobacterial disease.

We hope you find our selection for HIV/AIDS Research Review stimulating reading, and we welcome your feedback. Furthermore, if you have discovered or been involved in what you think is significant global research, please let us know and we will consider it for inclusion next time.

Kind Regards,

Dr Darren Russell

darren.russell@researchreview.com.au

Ten-year safety with polyacrylamide gel used to correct facial lipoatrophy in HIV-infected patients

Authors: Negredo E et al.

Summary: This cross-sectional study involving 751 patients investigated the long-term safety of polyacrylamide hydrogel [Aquamid®] for the repair of facial lipoatrophy. A total of 104 patients were identified who had received Aquamid® inflitrations at least 10 years prior. Of these patients, 24.0% had very severe facial lipoatrophy, 41.3% had severe facial lipoatrophy and 34.7% had moderate facial lipoatrophy at baseline. At a mean of 10.3 years of follow-up, 19.2%, 47.7% and 31.7% of patients reported moderate, mild, and no signs of facial lipoatrophy; corresponding percentages reported by physicians were 1.9%, 10.6%, and 87.5%. Among the 104 patients, 3.8% developed nodules, 6.7% developed indurations and 4.8% experienced local infection. Among those patients with a shorter follow-up (<10 years), 15 experienced local infections, with three requiring removal of Aquamid®. The overall incidence of local infection was 2.7%. Among all patients, 74.8% reported that they were highly satisfied and 23.4% were satisfied with the cosmetic results obtained with the agent; among those with severe or very severe lipoatrophy at baseline, the rates were 65.7% and 31.4%, respectively.

Comment: Facial lipoatrophy can be a distressing condition for people living with HIV but fortunately it is no longer seen very often. Those treated with older antiretroviral regimens are most at risk and polylactic acid [Sculptra®] is available on the Pharmaceutical Benefits Scheme (PBS) to treat it. This study reported on >10 year follow-up in those who had used the injectable polyacrylamide hydrogel [Aquamid®]. High satisfaction levels were reported over many years with few significant side effects. This gives reassurance for those using this product and suggests polyacrylamide hydrogel might be a good alternative to the use of polylactic acid, though in Australia the latter would have a strong financial advantage in those eligible for the PBS subsidy.

Reference: AIDS Res Hum Retroviruses 2015;31(8):817-21

Abstract

Antiretroviral activity and safety of once-daily etravirine in treatment-naive HIV-infected adults: 48-week results

Authors: Floris-Moore MA et al.

Summary: This single arm, open-label study investigated the antiretroviral activity, safety and tolerability of once-daily etravirine in 79 treatment-naïve HIV-infected adults (median age 29 years; 90% male; baseline median HIV-1 RNA 4.52 log_{10} copies/mL). All patients received etravirine 400 mg plus tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) 300/200mg once daily. Of 69 patients followed up at 48 weeks, 61 (77%) achieved an HIV-1 RNA level of <50 copies/mL. Among those with virologic failure, genotypic resistance-associated mutations were detected in three. The median CD4+ cell count increase was 163 cells/uL. A new sign/symptom or lab abnormality ≥ Grade 3 occurred in 15 (19.0%) participants and three (3.8%) permanently discontinued etravirine due to toxicity. Two patients experienced psychiatric symptoms. No deaths occurred during the study period.

Comment: Etravirine is a useful agent as part of the antiretroviral armamentarium, though the US Department of Health and Human Services (DHHS) Guidelines do not recommend its use first-line due to a lack of evidence in this population. As such, it tends to be used in those who cannot tolerate other regimens, or as part of a salvage regimen. The requirement for twice-daily dosing hasn't helped the uptake of this drug, either, despite its good side-effect profile and relative hardiness when it comes to resistance. This small, open-label study showed etravirine to be safe and effective, and suggests it may have a place in the treatment of antiretroviral-naïve individuals, though larger, comparative studies would be required to have greater confidence in its use. Furthermore, etravirine is not PBS reimbursed for first-line therapy, which may constitute an even larger barrier to its increased usage in Australia.

Reference: Antivir Ther. 2015;Aug 11 [Epub ahead of print]
Abstract

Low bone mineral density and risk of incident fracture in HIV-infected adults

Authors: Battalora L et al.

Summary: The relationship between low bone mineral density (T-score in the interval >-2.5 to <-1.0 [osteopaenia], or ≤-2.5 [osteoporosis]) and incident fractures in HIV-infected individuals was investigated in this study involving participants in two HIV cohort studies. During 2004 to 2012, dual energy x-ray absorptiometry (DXA) results of the femoral neck of the hip and clinical data were obtained prospectively and the findings analysed for 1006 individuals (median age 43 years, 83% male, 67% non-Hispanic white, median CD4+ cell count 461 cells/mm^3). Overall, 36% of participants had osteopaenia and 4% had osteoporosis; 67 had a prior fracture documented. During 4068 person-years of observation after DXA scanning, 85 incident fractures occurred, predominantly rib/sternum (n = 18), hand (n = 14), foot (n = 13) and wrist (n = 11). Multivariable proportional hazards regression analysis revealed that osteoporosis and current/prior tobacco use were associated with incident fracture; adjusted HRs 4.02 (95% CI 2.02-8.01) and 1.59 (95% CI 1.02-2.50), respectively.

Comment: This large sample of people living with HIV in the US followed prospectively demonstrates a strong association between osteoporosis and subsequent fracture risk. This is hardly surprising, but does provide much-needed data in this population group. The authors also found an association between smoking and incident fracture, which gives even more weight (if any were needed) to the strong moves to reduce the prevalence of smoking in PLHIV. With comprehensive, evidence-based guidelines published online in Clinical Infectious Diseases in January of this year, the way is open to better manage the risk of osteoporosis and fractures in our PLHIV. FRAX scores are readily available online, with recommendations to screen PLHIV over the age of 40. Access to affordable DXA scanning, though, can be problematic in Australia, though FRAX scores can be calculated without bone mineral density scanning having been performed and are likely to be of increased utility in our ageing HIV population.

Reference: Antivir Ther. 2015;Jul 21 [Epub ahead of print]
Abstract

Independent commentary by Dr Darren Russell

Darren is a sexual health physician at Cairns Hospital and holds the positions of Clinical Associate Professor at The University of Melbourne and Adjunct Associate Professor at James Cook University. He also chairs the HIV Foundation Queensland.

Long-term immunologic and virologic responses on raltegravir-containing regimens among ART-experienced participants in the HIV Outpatient Study

Authors: Buchacz K et al.

Summary: This study retrospectively analysed data from ART-experienced HIV participants enrolled in the HIV outpatient study (HOPS), to examine long-term outcomes of raltegravir-containing (n = 472) versus raltegravir-sparing ART (n = 472; propensity matched) in routine HIV care. Baseline clinical data were similar between the raltegravir-exposed (mean nadir CD4 205 cells/mm^3; mean baseline CD4 460 cells/mm^3; HIV RNA <50 copies/mL in 61% of patients; mean period on ART 7.5 years) and raltegravir-unexposed patients. Mortality rates, immunological and virological trajectories did not differ between groups over a 3-year follow-up period. In patients with detectable baseline HIV RNA levels, 76% of raltegravir-exposed and 63% of raltegravir-unexposed patients achieved HIV RNA <50 copies/mL and CD4 counts increased by ≥50 cells/mm^3 in 69% and 58% of patients.

Comment: This large, retrospective, cohort study from the US suggests that real-life usage of the integrase inhibitor, raltegravir, produces similar outcomes to those on other treatments. While somewhat reassuring, the STARTMRK study (published in 2013) produced 5-year data comparing raltegravir-based to efavirenz-based therapy and showed superior efficacy for the former. This was largely on the basis of reduced neuropsychiatric side effects, which are more common in those taking efavirenz. Still, real-world outpatient data are welcome and provide more evidence for the usage of integrase-based regimens, consistent with the most recent DHHS and Australian treatment guidelines. Rapid virological suppression, a clean side-effect profile, and few drug-drug interactions for raltegravir ensure that it has a place at the table when it comes to commencing treatment in the modern era.

Reference: HIV Clin Trials 2015;16(4):139-46
Abstract

Regimen selection in the OPTIONS trial of HIV salvage therapy: drug resistance, prior therapy, and race-ethnicity determine the degree of regimen complexity

Authors: Tashima KT et al.

Summary: In this US paper, the selection of a regimen for using a web-based utility to facilitate treatment recommendations for highly treatment-experienced patients (n = 413) is examined. The first or second recommended regimen was initiated in 86% of patients while a complex regimen was initiated in 21% of patients. Multivariate analysis indicated that selection of a complex regimen was associated with ART resistance to NRTIs (OR 2.2), NNRTIs (OR 6.2) or boosted protease inhibitors (OR 6.6), the prior use of integrase strand transfer inhibitors (OR 25), and race/ethnicity (all p ≤ 0.01). Black non-Hispanic (OR 0.5) and Hispanic participants (OR 0.2) were less likely to start a complex regimen, compared to white non-Hispanic participants.

Comment: We hear less about salvage therapy for HIV nowadays, probably due to the marked improvement in efficacy, tolerability and 'forgiveness' of regimens over the last 20 years, along with the fact that virtually no one will have commenced a one- or two-drug regimen in recent years. Patients requiring salvage therapy still exist, however, and the decision-making is complex for clinicians when it comes to selecting an optimal treatment regimen. This relatively large study of 413 participants used a web-based utility to aid decision-making and found that prior drug resistance, prior integrase inhibitor use, and race/ethnicity were key factors in decisions to select a more complex regimen. Enfuvirtide was among the antiretrovirals used, along with tipranavir - two agents that are very rarely used in modern treatment regimens.

Reference: HIV Clin Trials. 2015;16(4):147-56
Abstract

Disparities in initiation of combination antiretroviral treatment and in virologic suppression among patients in the HIV outpatient study, 2000-2013

Authors: Novak RM et al.

Summary: This analysis of data from participants in the antiretroviral-naïve HIV Outpatient Study, enrolled within 6 months of diagnosis (n = 1156; median age 37 years, 43.2% non-Hispanic/Latino black, 14.1% Hispanic/Latino), examined temporal trends and disparities in time to initiation of combination-ART and virological suppression (<500 copies/mL). Estimated median time from diagnosis to combination-ART initiation and virological suppression declined by >40% to 2.5 and 5.4 months over the 13.5-year study period. Multivariate analyses indicated that non-Hispanic/Latino black patients and those who had injected drugs were slower to initiate combination-ART. After adjustment for CD4 cell count and viral load at treatment initiation, non-Hispanic/Latino black patients and those <30 years of age exhibited lower rates of virological suppression.

Comment: With Australia signed up to the United Nations 90-90-90 goals for HIV treatment, achieving these ambitious targets remains a challenge. The treatment cascade for the US has been shown to be disappointing, particularly with regards to retention in care. The Australian 2014 HIV Surveillance report estimated that only 73% of PLHIV who were diagnosed were on ART, despite good retention in care, at least compared to the US. This study showed that racial background, young age, and the use of injection drugs were associated with less favourable outcomes over the 13.5-year study period. Virological suppression should be attainable nowadays for all PLHIV, and extra supports may need to be provided for those who are marginalised in some way. This study provides more evidence as to where some of those extra supports should be directed.

Reference: J Acquir Immune Defic Syndr. 2015;70(1):23-32
Abstract

Pharmacokinetics of once versus twice daily darunavir in pregnant HIV-infected women

Authors: Stek A et al.

Summary: The International Maternal Pediatric Adolescent AIDS Clinical Trials Network Protocol P1026s is a prospective non-blind, pharmacokinetic study in HIV-infected pregnant women receiving darunavir /ritonavir 800 mg/100 mg once daily or 600 mg/100 mg twice daily. Analysis of pharmacokinetic data from 64 women revealed that for both regimens, the median darunavir AUC and the maximum concentration were reduced during pregnancy versus postpartum. The last measurable darunavir concentration was also reduced in pregnant women receiving once daily darunavir. In patients receiving the once daily regimen, the darunavir AUC was reduced by 38% during the second trimester and by 39% during the third trimester. In those receiving darunavir twice daily, the AUC was reduced by 26% in both trimesters. In 32 paired samples, the median cord blood/maternal darunavir concentration ratio was 0.18.

Comment: Recent changes to the DHHS Treatment Guidelines for pregnant women has seen darunavir/r moved to being a preferred treatment option (along with two NRTIs) as it is better tolerated than lopinavir/r (which has now moved to the status of being an alternative regimen). The guidelines recommend twice-daily administration for darunavir/r. This study of 64 pregnant women suggests that an increased twice-daily dose may in fact be necessary due to the unfavourable pharmacokinetics for darunavir/r in pregnancy. There are still no data on the use of atazanavir or darunavir with cobicistat in pregnancy, so neither of these combinations can yet be recommend for use in pregnancy. Such data will be keenly awaited.

Reference: J Acquir Immune Defic Syndr. 2015;70(1):33-41
Abstract

Cellular immune correlates analysis of an HIV-1 preexposure prophylaxis trial

Authors: Kuebler PJ et al.

Summary: The Preexposure Prophylaxis Initiative (iPrEx) chemoprophylaxis trial included a case-control immunology study of HIV-1-specific T-cell responses in exposed seronegative subjects. 84 pre-infection peripheral blood mononuclear cell samples in patients who later seroconverted were matched with 480 samples from patients in both the placebo and active treatment arms who remained seronegative. IFN-γ responses varied across subjects; positive responses for Gag ($p = 0.007$), integrase ($p < 0.001$), Vif ($p < 0.001$), and Nef ($p < 0.001$) antigens were more common in persistently HIV-1-negative patients. Vif- and integrase-specific T-cell responses were correlated with a lower HIV-1 infection risk (HR 0.36; 95% CI 0.19-0.66 and HR 0.52; 95% CI 0.28-0.96). IFN-γ secretion was largely attributed to effector memory CD4+ or CD8+ T cells.

Comment: With the World Health Organization now recommending gay men consider using PrEP for HIV prevention, and the numbers of people taking PrEP increasing rapidly, this study is timely. The authors conducted a large case-control immunology study of participants in the Preexposure Prophylaxis Initiative (iPrEx) chemoprophylaxis trial (which showed that daily tenofovir/emtricitabine is highly protective against HIV infection), selecting pre-infection time points for those who became infected compared with persistently HIV-1-negative controls. They confirmed that HIV-1–specific responses are present in exposed uninfected individuals, sometimes at very high magnitude. These HIV1–specific responses also correlated with infection risk.

Reference: Proc Natl Acad Sci U S A. 2015;112(27):8379-84
Abstract

Safety, tolerability and pharmacokinetics of rilpivirine following administration of a long-acting formulation in healthy volunteers

Authors: Verloes R et al.

Summary: A phase I study (NCT01031589) in healthy volunteers examined the pharmacokinetics of a long-acting rilpivirine formulation administered by intramuscular injections through single (open-label 300 mg [n =6] or 600 mg [n = 5]) and multiple (double-blind, randomised administration every 4 weeks of 1200, 600, and 600 mg [n = 6] or placebo [n = 2]) regimens. Grade 1 or 2 rilpivirine-related adverse events were rash, musculoskeletal stiffness and injection site reactions. After a single 300, 600 or 1200 mg injection, the mean maximum plasma concentrations were 39, 48 and 140 ng/mL, and the mean AUCs (over 28 days) were 17,090, 25,240 and 55,350 ng h/mL. Rilpivirine pharmacokinetics after the 1200 mg injection and each of the subsequent 600 mg injections were similar. The mean plasma concentration across the 28-day interval after the last injection in the multiple injection1200/600/600 mg regimen was 79 ng/mL.

Comment: With daily oral administration of antiretrovirals now simple, tolerable and effective, the search for longer-acting agents has commenced. These agents may have a role to play in treatment (potentially long-acting rilpivirine plus cabotegravir, an integrase inhibitor similar to dolutegravir), or as a long-acting injectable agent for pre-exposure prophylaxis in those who would prefer a long-acting agent, or in those who are unable to adhere to daily oral administration. This Phase I study demonstrated favourable tolerability and adequate plasma concentrations of injectable rilpivirine. Questions remain with regards to these injectable agents, particularly with regards to the 'tail' as plasma drug levels drop off after some months if the drug is not readministered. Will these low and tapering levels allow resistance to occur in those living with HIV, or allow infection and possible resistance to occur when used for PrEP? Despite these misgivings, research continues to find suitable agents that can be injected every 1-3 months with high efficacy and tolerability.

Reference: HIV Med. 2015;16(8):477-84
Abstract

Trends in nontuberculous mycobacterial disease in hospitalized subjects in Spain (1997–2010) according to HIV infection

Authors: Álvaro-Meca A et al.

Summary: This retrospective study used data from the Minimum Basic Data Set provided by the Spanish Ministry of Health in order to estimate the incidence of nontuberculous mycobacterial (NTM) disease in hospitalised patients, the rate of NTM disease-related mortality and to estimate trends in these variables according to HIV infection between 1997 and 2010. A total of 3729 incident cases of NMT were identified from the database (1934 in the HIV-positive group and 1795 in the HIV-negative group) among whom 602 deaths occurred, 379 in the HIV-positive group and 223 in the HIV-negative group. Both the incidence of NTM disease and the rate of NTM disease-related mortality were 1000-fold higher in the HIV-positive group compared with the HIV-negative group. While the incidence of NTM disease significantly ($p < 0.001$) decreased from 2.29 to 0.71 events/1000 patient-years from 1997-1999 to 2004-2010 in the HIV-positive group, the incidence increased significantly ($p < 0.001$) from 2.91 to 3.97 events/1000000 patient-years for the corresponding time periods in the HIV-negative group. During the same time periods, the HIV-positive group experienced a significant ($p < 0.001$) decrease in mortality from 4.28 to 1.39 events/10000 patient-years, while the HIV-negative group experienced a significant ($p = 0.059$) increase in mortality from 2.63 to 4.26 events per 10000000/patient-years, and then the rate stabilised at around 3.87 events per 10000000 patient-years ($p = 0.128$).

Comment: NTM was very common in the pre-ART era, was a significant cause of morbidity and was also shown to be associated with increased mortality in those with AIDS. It is seen rarely these days as people living with HIV commence ART early and avoid a low CD4 nadir. This large, retrospective study from Spain documents the change over the era when triple combination therapy became the norm, with a drop in incidence of NTM and an associated fall in mortality rates for those with HIV from 1997-2010. Interestingly, though, for those without HIV the incidence of NTM and its associated mortality increased over the same time period.

Reference: HIV Med. 2015;16(8):485-93
Abstract

Research Reviews are prepared with an independent commentary from relevant specialists. To become a reviewer please email geoff@researchreview.com.au

Research Review Australia Pty Ltd is an independent Australian publisher. Research Review receives funding from a variety of sources including Government depts., health product companies, insurers and other organisations with an interest in health. Journal content is created independently of sponsor companies with assistance from leading local specialists.

Privacy Policy: Research Review will record your email details on a secure database and will not release them to anyone without your prior approval. Research Review and you have the right to inspect, update or delete your details at any time. **Disclaimer:** This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

Research Review publications are intended for Australian health professionals.

RESEARCH REVIEW the Australian perspective

