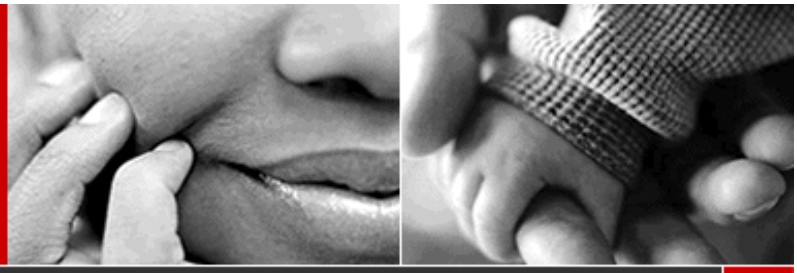

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Healthcare Professional Newsletter

December 2012 – Issue 33

Practice Point – "Lipodystrophy" due to an unexpected drug interaction

New symptoms are often attributed to the antiretroviral therapy (ART) a patient may be taking. It is important to consider the possibility of other causes, including unexpected drug interactions.

A 36 year old female patient who was on Truvada® and Aluvia® for 3 years with a suppressed viral load saw her GP because of increasing facial swelling for 3 months, which he thought was due to lipodystrophy as a result of the ART.

Claims analysis revealed that she had been taking a fluticasone nasal spray and oral antistamines for chronic sinusitis and allergic rhinitis for a number of months.

Aluvia® includes a low dose of ritonavir, which is a potent inhibitor of hepatic cytochrome P450 3A4 isoenzymes. Inhaled or intranasal fluticasone is known to interact with ritonavir, resulting in steroid accumulation and possible Cushing's syndrome[1]. It was felt this was a more likely cause for the facial swelling than lipodystrophy

The GP was advised to slowly withdraw the fluticasone spray and the facial swelling gradually resolved.

Significant systemic absorption may occur with topical steroid preparations, especially if over-used. Doctors are advised to review all medication when patients present with unexpected symptoms or signs and to always consider the possibility of drug interactions, particularly in patients taking boosted protease inhibitors.

Reference

1. Foisy MM, Yakiwchuk EMK, Chiu I, Singh AE. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. *HIV Med* 2008; 9: 389-396.

AfA Clinical Guidelines 9th edition

The 9th edition of the AfA Clinical Guidelines is now available. Please send us an email (afa@afadm.co.za) with your postal address or phone 0860 100 646 if you would like us to send you a free copy. Alternatively, the guidelines can be downloaded from the AfA website (www.aidforaids.co.za).

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Timing of ART in patients with cryptococcal meningitis

The majority of patients presenting with HIV-associated cryptococcal meningitis have low CD4 counts and are at high risk for other opportunistic infections. There is thus an urgency to start ART, but this needs to be counterbalanced by the risk of paradoxical cryptococcal immune reconstitution inflammatory syndrome (IRIS) after starting ART. It is estimated that around 20% of patients with cryptococcal meningitis starting ART develop IRIS which manifests with recurrent headache, other neurological manifestations and raised intracranial pressure. Approximately 20% of patients who develop cryptococcal IRIS die[1].

Decisions regarding the optimal timing of ART to maximize survival need to take into account these competing risks. Three clinical trials addressing this issue have been conducted. In a small trial conducted in Zimbabwe[2] amongst patients treated for cryptoccal meningitis with fluconazole alone (no amphotericin B) the mortality was significantly higher in those who started ART within 3 days of cryptococcal diagnosis compared with those who started 10 weeks after diagnosis. In contrast, a sub-group analysis of the ACTG A5164 trial[3] suggested reduced death and AIDS progression amongst cryptococcal meningitis patients who started ART around 2 weeks compared to those who deferred to around 6 weeks although these results were not significant.

The Cryptococcal Optimal ART Timing (COAT) trial was stopped by the DSMB earlier this year because of significantly higher mortality in those patients with cryptococcal meningitis who started ART while in hospital. This trial was conducted in Uganda and South Africa and enrolled ART-naïve patients with cryptococcal meningitis who were randomized to start ART 1-2 weeks after cryptococcal diagnosis (while still in hospital) or defer until 5-6 weeks (generally as an outpatient). All patients were treated initially with amphotericin B-based therapy in this trial. After 177 participants (of a planned 500) were enrolled the trial was stopped because of a significantly increased risk of mortality in the early arm (42.5% vs 27.6%). The majority of the excess deaths were in the first month of ART. For further details see: http://www.niaid.nih.gov/news/QA/Pages/COATqa.aspx. Full results from this trial will be presented in 2013.

Based on the findings of the COAT trial we suggest that ART should not be started while patients with cryptococcal meningitis are still receiving their induction therapy with amphotericin B, but should be deferred until 4-6 weeks after cryptococcal diagnosis.

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1. Muller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: A systematic review and meta-analysis. *Lancet Infect Dis* 2010;10:251-261.
2. Makadzange AT, Ndhlovu CE, Takarinda K, Reid M, Kurangwa M, Gona P, Hakim JG. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-Saharan Africa. *Clin Infect Dis* 2010;50:1532-1538.
3. Zolopa A, Andersen J, Powderly W, Sanchez A, Sanne I, Suckow C, Hogg E, Komarow L. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: A multicenter randomized strategy trial. *PLoS One* 2009;4:e5575.

GEMS HIV Disease Management Programme (DMP): Important information

Please note that the GEMS HIV DMP will change from 01 January 2013. The new contact details will be 0860GEMSDM (086 043 67 36) and 0800GEMSFAX (0800 436 73 29).

Abacavir or Tenofovir in 1ST line ART?

Abacavir (ABC) and tenofovir (TDF) are nucleoside reverse transcriptase inhibitors (NRTIs) with a low risk of toxicity. Specifically, both drugs are relatively free of mitochondrial toxicity, which is responsible for lipoatrophy and hyperlactataemia. Both drugs have long half-lives, allowing for once daily dosage, and both are available as fixed dose combinations with other NRTIs.

Although both ABC and TDF are generally well tolerated, they both can cause severe adverse drug reactions. Nephrotoxicity is the major adverse drug reaction of TDF, and it is not recommended in patients with renal impairment, although it can be used in reduced doses in selected patients with renal failure. ABC may cause a life-threatening systemic hypersensitivity, which is genetically determined, being confined to people who are HLA-B*5701 positive. However, this HLA type is uncommon in Sub Saharan Africa: a study from the UK[1] reported a prevalence of 7.93% in white patients and 0.26% in black patients. An increased risk of myocardial infarction has been reported in patients starting ABC in cohort studies, but this was not found in a meta-analysis of RCTs[2] that specifically examined the risk of cardiovascular events.

Two randomised controlled trials have compared the efficacy of TDF (plus emtricitabine, TDF+FTC) with ABC (plus lamivudine, ABC+3TC) as the dual NRTI backbone of ART regimens. In the ACTG A5202 study 1858 patients were randomised to ABC+3TC or TDF+FTC given in combination with either efavirenz or ritonavir-boosted atazanavir. Randomisation was stratified by baseline viral load above or below 100,000 copies/mL. An interim analysis showed more virologic failures in patients randomised to ABC+3TC whose baseline viral loads were ≥100,000 copies/mL[3]. The final analysis of the ACTG A5202 study showed that ABC+3TC was equivalent to TDF+FTC in patients with a baseline viral load <100,000 copies/mL[4]. In the ASSERT study 385 patients were randomised to ABC+3TC or TDF+FTC, both given together with efavirenz. A lower proportion of patients randomised to ABC+3TC achieved a viral load <50 copies/ml than TDF+FTC (59% versus 71% with a difference of 11.6%; 95% CI 2.2 to 21.2%)[5]. Higher rates of virologic failure with ABC+3TC did not seem to be confined to patients with high baseline viral loads, but the study lacked power for this subanalysis.

By contrast, zidovudine (ZDV) had similar efficacy to TDF in the PEARLS study, but more toxicity[6]. AfA recommends ZDV in patients with renal impairment or unable to tolerate TDF. ABC is recommended only if ZDV is not tolerated (or is contraindicated). ABC is best avoided in patients with high baseline viral loads.

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1. Orkin C, Sadiq ST, Rice L, Jackson F; UK EPI team. Prospective epidemiological study of the prevalence of human leukocyte antigen (HLA)-B*5701 in HIV-1-infected UK subjects. HIV Med. 2010;11(3):187-92.
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4. Sax PE, Tierney C, Collier AC, et al. Abacavir/lamivudine versus tenofovir DF/emtricitabine as part of combination regimens for initial treatment of HIV: final results. J Infect Dis. 2011;204(8):1191-201.
5. Post FA, Moyle GJ, Stellbrink HJ, Domingo P, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. J Acquir Immune Defic Syndr. 2010;55(1):49-57.
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The Medscheme Reference price for ABC 300mg (60 tablets) is R731.24 and TDF 300mg (30 Tablets) is R215.41

Correction to Aid for AIDS Healthcare Professional Newsletter - Issue 32

Please note that there was an error on page 4 of the last newsletter. In the paragraph titled “What monitoring is necessary for children”, the units given for the modified Counahan-Barrat formula are incorrect. The correct formula is: GFR = 40 x Height (cm) / Serum Creatinine (µmol/l). We apologise for any inconvenience caused by this error.

A Festive Reflection - Prof. Marc Mendelson

I must admit that I have always met the statement “the condom burst” with a fair degree of scepticism, taking it as a euphemism for ‘I didn’t wear one’. Back in the day, this was not a common experience that was discussed down the pub, although granted, men feel more able to own up to embarrassing experiences since Pele went on TV to tell us it was OK to talk about erectile dysfunction. So I was interested to learn that despite manufacturers formidable and stringent tests of tensile strength (pictured below), a number of publications show that breakage rates amongst men using condoms are high.

A study of young men 17-22 years using condoms, reported 23% experiencing at least one breakage during the prior 12 months and 2.5% of all condoms had broken[1]. Multivariate analysis showed that increased experience of condom use protected against breakage. Another study in Sydney of 108 men aged 18-62 years, documented an overall breakage rate of 4.9%[2]. Risk factors for breakage in multivariate analysis were male sex partner(s), infrequent condom use, having trouble with condoms slipping, and interestingly, use of the conventional application method of rolling the condom on. Modified application methods appeared protective. Clearly, condom breakage is not merely a euphemism, and perhaps we need to spend a bit more time counselling our patients about condom use, so that they don’t go into battle unprepared. Both studies identified experience with condoms as protective, so maybe it’s time to bring back that wooden phallus and get teaching, or set up virtual reality programmes to save our young men and women from a damp squib. My New Year’s resolution is to devote the next year of my life to understanding the mechanisms of condom breakage. Not since Kinsey will there have been a study like it, carefully documenting controlled explosions in the South African boudoir and beyond. Donations to fund this important work gratefully received.

References

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