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**Incorrect attribution of cerebrospinal fluid HIV-1 virological escape and lymphocytic meningitis to lopinavir/ritonavir monotherapy**

We respectfully disagree with many of the interpretations of the case reported by de Truchis *et al.* [1] entitled ‘Cerebrospinal fluid HIV-1 virological escape with lymphocytic meningitis under lopinavir/ritonavir monotherapy’.

The title is misleading. Many readers might interpret that ‘escape’ means that HIV replication was suppressed in blood and active in the cerebrospinal fluid (CSF). This is not the case as the patient at the time of presentation had active replication both in blood and CSF.

The patient was inadequately treated with lopinavir/ritonavir monotherapy. Authors do not emphasize enough that, as recommended in the European AIDS Clinical Society (EACS) guidelines [2], patients infected with protease inhibitor-resistant isolates should not be treated with lopinavir/ritonavir monotherapy. All the trials of protease inhibitor monotherapy have excluded patients who might be infected with HIV isolates resistant to protease inhibitors. It is interesting, however, that in Truchis *et al.* [1] case, virological suppression was achieved during 18 months despite intermediate resistance to lopinavir/ritonavir. Once again, this finding supports the extremely high genetic barrier to resistance of boosted protease inhibitors.

Virological failure and lymphocytic meningitis is wrongly attributed to the use of lopinavir/ritonavir monotherapy. It is very likely that the reduction of plasmatic and CSF levels of lopinavir/ritonavir concentrations possibly caused by orlistat would have not changed if the patient had been treated with two analogs and lopinavir/ritonavir with similar clinical consequences and with the additional possible development of resistance to nucleosides.

The authors claim discordant viral evolution in CSF without adequate data. There is no CSF sample to prove that an isolate with 54V was also present in CSF at the time the first resistance testing was performed in plasma. An alternative explanation is disappearance of 54V both in plasma and CSF owing to insufficient drug pressure caused by low levels of lopinavir/ritonavir. Nevertheless, discordant viral evolution in the CSF and higher viral loads in CSF than in plasma have also been described in patients receiving triple therapy [3].

The authors incorrectly quote Monotherapy Switzerland Thailand (MOST) study of Gutmann *et al.* [4] as supporting evidence of a higher risk of discordant replication in CSF in patients treated with boosted protease inhibitor monotherapy. In the MOST study, all six patients with neurological symptoms had virological failure both in blood and CSF.

The authors mention the studies of Gutmann *et al.* [4] and Katlama *et al.* [5] as evidence of a higher risk of HIV encephalitis in patients treated with monotherapy but omit to mention that this complication also occurs in patients treated with triple therapy [3].

Until we have a randomized clinical trial that systematically evaluates CSF replication in patients treated with boosted protease inhibitor monotherapy versus triple therapy, claims of ‘a higher risk of virological escape under protease inhibitor monotherapy’ would not be based on adequate evidence. Finally, we recommend that clinicians closely follow the EACS guidelines [2] before switching patients to boosted protease inhibitor monotherapy.

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**References**


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High neonatal concentrations of raltegravir following transplacental transfer in HIV-1 positive pregnant women

Raltegravir, an integrase inhibitor, used in the treatment of triple class resistant HIV-1, causes rapid reduction in HIV-1 viral load and is usually well tolerated. Principally metabolized by UGT1A1-mediated glucuronidation, it neither inhibits cytochrome P450 (CYP450) enzymes nor induces CYP3A4, giving it a favourable drug interaction profile [1–3]. These features make raltegravir a useful option for pregnant women who present late or have drug-resistant HIV-1. Little is known about human transplacental transfer of raltegravir, neonatal pharmacokinetics and safety.

We report three cases in which raltegravir was used late in pregnancy to rapidly reduce maternal HIV-1 viral load (Roche Taqman 2.0 assay), in women with multidrug resistant virus. Blood samples were taken from mother and baby as close to delivery as possible and maternal viral load was monitored up to delivery. Neonates were assessed by HIV-1 DNA PCR at 0, 6, and 12 weeks.

Table 1. Summary of case study results.

<table>
<thead>
<tr>
<th>Case</th>
<th>One</th>
<th>Two</th>
<th>Three</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI mutations</td>
<td>I54M, M46M/I, V82A, L90M (accumulation of multiple tests)</td>
<td>M46I/M, L90M (baseline resistance at diagnosis)</td>
<td>Nil known (no resistance tests)</td>
</tr>
<tr>
<td>Gestation RAL initiated</td>
<td>28 weeks</td>
<td>38 weeks</td>
<td>39 weeks</td>
</tr>
<tr>
<td>VL at RAL initiation</td>
<td>183</td>
<td>67100</td>
<td>238</td>
</tr>
<tr>
<td>Other ARV in regimen</td>
<td>Tenofovir/emtricitabine, abacavir etravirine</td>
<td>Tenofovir/emtricitabine, darunavir/ritonavir, (IV zidovudine at delivery)</td>
<td>Tenofovir/emtricitabine, efavirenz (IV zidovudine at delivery)</td>
</tr>
<tr>
<td>Delivery mode</td>
<td>Elective CS 39 weeks</td>
<td>Emergency CS 40 weeks + 3 days</td>
<td>Elective CS 40 weeks + 1 day</td>
</tr>
<tr>
<td>Delivery VL</td>
<td>&lt;40</td>
<td>185 (4 days prior to delivery)</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Mother RAL concentration (ng/ml)</td>
<td>493</td>
<td>22</td>
<td>50</td>
</tr>
<tr>
<td>Time postmaternal dose (h)</td>
<td>7</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Time after delivery (h)</td>
<td>3</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Baby RAL concentration (ng/ml)</td>
<td>3634</td>
<td>209</td>
<td>776 and 5</td>
</tr>
<tr>
<td>Time postmaternal dose (h)</td>
<td>7</td>
<td>13</td>
<td>5.5</td>
</tr>
<tr>
<td>Time after delivery (h)</td>
<td>3</td>
<td>1</td>
<td>2.5 and 72</td>
</tr>
<tr>
<td>Baby ARV postpartum for 1 month</td>
<td>Zidovudine</td>
<td>Etravirine, lamivudine, darunavir/ritonavir enfuvirtide</td>
<td>Zidovudine lamivudine, lopinavir/ritonavir</td>
</tr>
</tbody>
</table>

ARV, antiretroviral; CS, caesarean section; IV, intravenous; PI, protease inhibitor; RAL, raltegravir; RT, reverse transcriptase; VL, HIV-1 viral load (copies/ml).
which improved after etravirine was stopped. Patient 3 was a 31-year-old Zimbabwean nulliparous woman with a history of nevirapine allergy, intolerance of protease inhibitors and poor adherence. At 29 weeks of gestation, because viral load was 3210 copies/ml, her prescription was changed from tenofovir/emtricitabine and lopinavir/ritonavir to efavirenz. At 39 weeks, viral load was still detectable and raltegravir was added.

Raltegravir concentrations, within 3 h after delivery, in the neonates of patients 1 and 2, were approximately 7 and 9.5 times higher than in the mothers’ paired samples, respectively. Paired samples were not collected for patient 3. However, neonatal concentrations were still high 2.5 h after delivery. All infants were HIV-1 DNA PCR negative at 12 weeks. To date, no adverse reactions in mother or child have been reported.

In all three cases, addition of raltegravir to the mother’s regimen was associated with rapid reduction in maternal viral load. The much higher raltegravir concentrations in neonates compared with their mothers suggests effective placental transfer, perhaps reflecting poor neonatal and foetal maturity of the UGT-dependent pathways [4]. It is possible that increased activity of UGT1A1 observed in pregnant women contributed to the disparity [5]. Reduced activity of UGT1A1 in neonates, probably resulting from low transcription levels rather than variation in UGT1A1 genotypes [4], is potentially more critical after placental separation because of the effects of placental dialysis. If, as in these cases, there are limited neonatal adverse effects associated with high raltegravir concentrations, it suggests potential favourable pharmacokinetics for preloading raltegravir in newborns. This could be important in the case of preterm neonates who absorb oral agents poorly. However, increases in UGT1A1 activity after birth may be related to birth-related events and not gestational age [4]. Neonatal raltegravir concentrations in patient 3 had fallen to subtherapeutic (<15 ng/ml) within 72 h of birth. Excretion of unchanged raltegravir in the urine and faeces may have been important here [2].

Placental transfer is also influenced by plasma protein binding and placental transporters [6]. Raltegravir is approximately 83% bound to plasma proteins [3], concentrations of which alter in pregnancy [6]. Protease inhibitors are more protein bound than raltegravir and transfer poorly across the placenta [6]. Raltegravir is a substrate of P-glycoprotein (PGP) [2], which is highly expressed in placental tissue and which appears to protect the foetus from maternal concentrations of drugs and metabolites [7]. Decreased PGP expression may increase foetal drug exposure. Potent drug-induced inhibition of placental PGP has been shown to increase transfer of the protease inhibitor, indinavir, but this effect was not achieved by ritonavir, which is also a PGP inhibitor [8]. Exploring the use of PGP inhibitors in pregnancy to increase foetal drug exposure may widen options for preventing mother-to-child transmission of HIV.

In conclusion, raltegravir was effectively transferred across the placenta of three pregnant women and persisted in neonates for up to 3 days, without adverse effects.

Acknowledgements

D.A.M. developed the analytical methodology and analysed the raltegravir concentrations for the samples collected from patients 1 and 3 and jointly drafted the manuscript. M.R. was a specialist registrar (attending physician), for patients 1 and 3 and jointly drafted the manuscript. S.D. is a paediatric clinical nurse specialist for patients 1 and 3. M.S. is a paediatric HIV consultant specialist for patients 1 and 3. D.W.H. is the Director of the Analytical Unit, where the analytical work was performed, and contributed to the manuscript. I.C. is a HIV consultant specialist for patient 2. P.H. jointly instigated the study and contributed to the content of the manuscript. He is the supervising HIV consultant specialist in charge for patients 1 and 3. S.T.S. jointly instigated the study, enabled local analysis of raltegravir concentrations and significantly contributed to the content of the manuscript.

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Data for patient 2 were presented as an oral at the Second Joint Conference of the British HIV Association (BHIVA) with the British Association for Sexual Health and HIV (BASHH), 20–23 April 2010, Manchester, UK. BHIVA/BASHH Workshop 4 on ‘Raltegravir: a niche in late pregnancy’ and the slides published on the BHIVA Website, www.bhiva.org.

Data for all three patients have been accepted as a poster presentation at the XVIII International AIDS Conference on ‘Raltegravir in the prevention of mother-to-child transmission of HIV: high concentrations demonstrated in newborns’, Vienna, Austria, 18–23 July 2010. The abstract will be published on CD-ROM and online.

Denise A. Mckeown, Melanie Rosenvinge, Sheila Donaghy, Mike Sharland, David W. Holt, Ian Cormack, Phillip Hay and S. Tariq Sadiq.

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Infectiousness of HIV-infected homosexual men in the era of highly active antiretroviral therapy

The recent study by Jin et al. [1] provides estimates of infectiousness of anal intercourse (insertive circumcised and uncircumcised; receptive with and without ejaculation) for the male homosexual population of Sydney, Australia, in the highly active antiretroviral therapy (HAART) era. There is a lack of estimates of HIV infectiousness for homosexual men and for anal intercourse in general and especially for infectiousness with treatment. A recent literature review [2] found only four studies reporting estimates of HIV transmissibility per anal intercourse act. Therefore, the additional data presented by Jin et al. [1] are an important contribution to the literature. There are many methodological challenges when quantifying HIV infectiousness, which have been discussed elsewhere [3,4]. Although the best study design for quantifying per-act HIV infectiousness for heterosexual populations has involved discordant monogamous couples (although compromised with its own set of biases), these types of study have been seldom used for homosexual populations. It may be more difficult to recruit such participants if rates of monogamy are lower than among heterosexual populations, and monogamous homosexual couples may also not be very representative of the wider male homosexual community. The alternative approach used by Jin et al. [1] was to follow up initially HIV-seronegative homosexual men, testing annually for seroconversion and interviewing every 6 months for reports of types and frequencies of sexual exposure and the presumed serostatus of their sexual partners (categorized as HIV negative, positive or unknown). A similar approach has been used before for anal intercourse by Vittinghoff et al. [5] as well as for female sex workers [6,7]. However, Vittinghoff et al. [5] were unable to provide per-act estimates per positive exposure for insertive anal intercourse, only providing estimates per-act with an ‘infected or unknown serostatus’ partner and, therefore, may underestimate infectiousness per exposure, if HIV prevalence among unknown serostatus partners is low.

The per-act anal intercourse transmission probability estimates of Jin et al. [1] with respect to receptive unprotected anal intercourse [0.65%, 95% confidence interval (CI) 0.15–1.53 with withdrawal; 1.43%, 95% CI 0.48–2.85 with ejaculation], from a population with high (proposed 70%) HAART coverage, are remarkably similar to those estimates made preceding HAART (summary of four estimates: 1.4%, 95% CI 0.2–2.5, no differentiation by ejaculation [2], see Fig. 1 [2,5,8–10]). As the authors note, this result is surprising, given the reduction in community viral load that has been observed in some other homosexual populations following the introduction of HAART [11], and that such reductions in viral load are expected to reduce HIV infectiousness.

Potential reasons why HIV infectiousness was not seen to decrease include higher infectiousness associated with various cofactors (sexually transmitted infection prevalence may be higher in male homosexual communities now, perhaps as a result of risk compensation in the HAART era); there may be unreported competing exposures through other routes of transmission, such as intravenous drug use; or the partners of study participants may not have been representative of the wider Australian homosexual population, for example, with lower HAART coverage. It would have been useful to have more information regarding the likely HAART coverage of the infected partners, in order to assess how concerning these unexpectedly high estimates for infectiousness are. Although the authors state that 70% of male homosexuals diagnosed in Australia are currently treated, estimates of the proportion of those infected who are diagnosed as well as an indication of adherence levels and average viral loads for those individuals receiving treatment are required to improve our understanding.

The authors addressed the uncertainty regarding ‘unknown’ serostatus and presumed HIV-negative sexual partners by undertaking uncertainty analysis, varying

References


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the HIV prevalence of the ‘unknown’ and presumed HIV-negative partner populations from 5–15% and 0.5–2%, respectively, based on prevalence studies from the locality. It would be informative if this analysis could be extended to reflect the uncertainty in HAART coverage levels in order to explore how sensitive the HIV infectiousness estimates are to the assumed proportion of sexual partners on treatment.

However, even in the absence of further information, levels of HAART are likely to be substantial and so the authors’ observation that their per-act estimates are not markedly different from those made in the absence of HAART remains a concerning finding. Community viral load studies covering the Sydney population may help to explain these findings, although the association between viral load and HIV infectiousness for sexual transmission, particularly for anal intercourse, remains to be definitively proven. It would also be useful, if data are available or for future cohorts, to ascertain the treatment status of infected partners wherever possible, in order to make estimates of anal intercourse infectiousness stratified by treatment status. This study and our review have clearly highlighted the need for more data on HIV infectiousness for sexual transmission among homosexual men [1,2].

Acknowledgement

There are no conflicts of interest.

References

Infectiousness of HIV-infected men who have sex with men in the era of highly active antiretroviral therapy

In the majority of resource-rich countries, the most common exposure route for HIV transmission is unprotected anal intercourse among homosexual men [1,2]. HIV diagnosis rates in these settings have been increasing over the last decade [1–3], which is somewhat paradoxical considering that effective combination antiretroviral therapy (ART) has had increasing coverage. There is evidence among heterosexuals of a positive association between viral load and infectiousness [4–6], and use of ART has been shown to reduce HIV transmission risk among discordant couples [7]. Further, both a recent meta-analysis [8] and a prospective cohort study [8] calculated a remarkably similar reduction, of 92%, in HIV transmission rates from heterosexual men and women who are treated compared with those who are untreated. It might be expected that ART would also reduce HIV transmission rates among homosexual men, but the fact that the per-contact probability of HIV transmission through anal intercourse is more than 10-fold higher than by vaginal intercourse means that results may not necessarily be the same.

The recent meta-analysis by Baggaley et al. [9] resulted in an estimate of the probability of HIV transmission through receptive anal intercourse of 1.4%, which aligns with our estimate from an Australian cohort of homosexual men [10]. It is surprising that these estimates of HIV transmission risk are also similar to estimates prior to the use of ART [11]. Our study is the first to differentiate the per-act probability of HIV transmission by receptive anal intercourse with or without ejaculation (1.43 and 0.65%, respectively) and insertive anal intercourse with or without circumcision (0.11 and 0.62%, respectively).

We agree with Baggaley et al. [12] that it would have been useful to have more information about highly active antiretroviral therapy (HAART) coverage among HIV-infected partners of the homosexual men in our cohort to elucidate the role of antiretrovirals in reducing transmission risk among homosexual men. However, the nature of many sexual partnerships among gay and other homosexual men is that information about partners is often limited. Information about treatment status is often known among discordant regular partners and, although disclosure of HIV serostatus is becoming increasingly common among casual partners [13–16], it is still not disclosed in most partnerships, let alone discussion of the use of ART. Collection of further detail, such as level of adherence to ART among partners of men in our cohort, was also beyond the scope of feasibility. In the absence of such data, we had to make assumptions that the partners had epidemiological and clinical characteristics that were similar to those captured by Australian surveillance mechanisms. Our calculations did not directly account for the proportion of the population on ART but estimated population average transmission rates resulting from HIV-infected people with a broad distribution of viral loads. Numerous sources justify an assumption that approximately 70% of Australia’s HIV-diagnosed population is on ART [17,18]. Australia’s HIV Observational Database tracks a large cohort of HIV-infected people and indicates that the degree of viral suppression among HIV-treated people has increased from ~65 in 2000 to ~90% currently, with an average of ~80% over the period of follow up in our cohort study [17]. However, the proportion of the HIV-infected population among Sydney homosexual men that is undiagnosed is not well known. Statistical and modeling calculations have estimated that consistently ~10% of HIV-infected men in Sydney are undiagnosed [19], which aligns with the relatively high testing rates in this population [18]. However, a recent study conducted in Melbourne has estimated that up to 20% of HIV-infected gay men in a comparable Australian context may be undiagnosed [20]. Taken together, it is quite possible that just 45–50% (80–90 x 70 x 80%) of HIV-infected homosexual men in Sydney had undetectable viral load during our study.

As this estimate shows, in a population with high rates of testing and treatment with highly effective antiretrovirals, it is likely that there are a substantial proportion of people with detectable viral load. This may go a long way toward accounting for the lack of difference in our estimates of transmission risks compared with the pre–HAART era.
However, one would still expect to find a noticeable decrease in average transmission risks owing to a reduction in average community viral load [21].

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