

THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

Antiretroviral News From the 45th ICAAC

By Joel E. Gallant, M.D., M.P.H.

The Katrina tragedy-cum-debacle resulted in the postponing of the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), originally scheduled to be held in New Orleans this fall. The conference was moved to Washington, DC, and despite the fact that it took place the week before Christmas, attendance was fairly high. The postponement of ICAAC meant that it would now be occurring less than two months before the Conference on Retroviruses and Opportunistic Infections (CROI), generally the most important scientific HIV conference of the year, and only one month after the Dublin EACS conference, which is covered in this issue. Nevertheless, we generally manage to glean some new data at each of the conferences, despite their frequency.

ACTG 5095

At ICAAC, Roy Gulick from Cornell presented long-awaited data from ACTG 5095 [Abstract H-416a]. Some readers might be thinking, "Long-awaited? Isn't 5095 old news?" It's true that the results of 5095 were presented in 2003 at the 2nd IAS conference in Paris [Abstract 41], and subsequently published in the *New England Journal of Medicine* [2004;350:1850-61]. However, those results involved only the comparison of the triple-nucleoside reverse transcriptase inhibitor (NRTI) arm, zidovudine/lamivudine/abacavir (AZT/3TC/ABC, *Trizivir*), versus the two combined, unblinded efavirenz (EFV) arms. The old news is that the triple-NRTI arm was stopped early because of a significantly greater rate of virologic failure; however, the other two arms of the trial continued, comparing EFV plus either AZT/3TC (*Combivir*) or AZT/3TC/ABC. As a reminder, this trial enrolled treatment-naïve patients with viral loads above 400 c/mL and no CD4 cell count entry criteria. Mean baseline viral load was 4.86 log₁₀ c/mL, and 43% had viral loads of at least 100,000 c/mL. Mean CD4 cell count at entry was 240 cells/mm³. A total of 765 patients were randomized to one of the two

EFV arms, of whom 78% completed the study. Two percent died, and 20% discontinued therapy, with no difference in discontinuation between arms. Median follow-up was 144 weeks.

The bottom line is that there was absolutely no difference between the two arms in terms of:

- Time to viral suppression (90% had viral loads below 200 c/mL by week 24).
- Virologic failure (25%).
- The percentage of patients achieving viral suppression to <200 or <50 c/mL.
- CD4 cell count response (an overall increase of approximately 300 cells/mm³).
- Time to virologic failure.
- Drug resistance among patients with no resistance at baseline. (Patients tended to fail with wild-type virus or with M184V, NNRTI mutations, or both. Thymidine analog mutations were uncommon.)

Finally, and perhaps most importantly, there was no difference in these endpoints when the analysis was restricted to patients with baseline viral loads above 100,000 c/mL. There was also no difference in grade 3-4 toxicity, though there was a difference in the frequency of presumed hypersensitivity reaction, which occurred in 10% of those on the 3-NRTI arm, but also in 7% of those on the 2-NRTI arm, highlighting the fact that the abacavir hypersensitivity reaction is often over-diagnosed.

One of the unexpected findings in this study came from the multivariate analysis looking at predictors of virologic failure. In that analysis, blacks were 1.67 times more likely to fail therapy than whites (P=0.003), and patients who had hepatitis C coinfection were 1.57 times more likely to

fail than those who did not (P=0.04). The investigators found that there was an interaction between race and adherence: blacks who self-reported non-adherence at 12 weeks had a significantly shorter time to virologic failure compared to adherent whites, blacks, or Hispanics or compared to whites and Hispanics reporting non-adherence. The reason for this surprising finding is unclear, but clearly needs to be teased out further with additional analyses of the adherence data. Potential reasons include different patterns of non-adherence (e.g. missed doses vs. longer or selective drug

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"Canadian Embassy," photograph by Joel Meneses

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interruptions) or genetic/racial difference in drug metabolism, potentially leading to higher EFV levels and greater toxicity among blacks compared to whites and Hispanics.

The results of ACTG 5095 finally put a critical question to rest: Is the standard, 3-drug regimen enough, especially in patients with high baseline viral loads or low CD4 counts? Apparently it is, at least if you're using a potent "anchor drug" like EFV. With the exception of a few more cases of abacavir hypersensitivity, the addition of a fourth agent (in this case, a third NRTI) didn't seem to do much harm, but it clearly didn't do any good, either. Together, these results and the disappointing results with NRTI-sparing regimens (see my EACS summary in this issue) suggest that we'll still be using two NRTIs plus a third agent for some time to come.

Enfuvirtide: Add it? Subtract it?

Speaking of more aggressive regimens, a study by Moltó and colleagues randomized 15 treatment-naïve patients with viral loads above 10,000 c/mL and no relevant resistance to receive either a combination of lopinavir/ritonavir (LPV/r), EFV, 3TC, and tenofovir DF (TDF) or the same combination plus enfuvirtide (ENF) [Abstract H-528]. They found a significant difference in the slope of viral load decline at day 2 favoring the ENF arm (-0.260 vs. -0.347 log₁₀ c/mL). By day 7, viral loads had declined from 5.1 to 3.98 logs in the control arm and from 4.98 to 3.55 logs in the ENF arm (P=0.06). The authors concluded that the addition of ENF to a potent 4-drug regimen increased potency by one-third. The clinical relevance of these findings is unclear, however. Does short-term potency translate into greater efficacy or durability? The results of ACTG 5095 suggest not, though we have not yet seen the data from 5095 looking at early viral decay dynamics. If those data show a more rapid decline in viral load in the 4-drug arm compared to the 3-drug arm, it will suggest that early antiretroviral potency is not necessarily associated with a better clinical outcome.

On the other hand, patients taking ENF can usually think of a number of reasons to stop taking it, and so can those who have to pay for it. But is it safe to stop ENF after viral suppression has been achieved? A

study presented at ICAAC randomized 18 patients with at least 9 months of virologic suppression on an ENF-based regimen to either discontinue ENF (N=8) or to continue it (N=10) [Bonjoch A, et al. Abstract H-527]. Patients in both arms continued the other drugs in their regimen. All 10 of the patients who continued ENF maintained virologic suppression, whereas 3 of the 8 patients who stopped ENF experienced virologic rebound. The authors concluded that stopping ENF is associated with an increased risk of early rebound. This study is obviously too small to determine statistical significance. However, the apparent difference between the two arms isn't surprising, given that most patients on ENF are on it for a reason: they frequently have few other suppressive options, and stopping ENF may leave them on an inadequate number of active drugs or on drugs that have only partial activity.

Once-Daily *Trizivir*/Tenofovir

Cal Cohen presented 48-week data on the previously presented COL40263 study, an uncontrolled trial of a 4-drug, all NRTI regimen of AZT/3TC/ABC plus tenofovir, administered once-daily at standard doses [Abstract H-521]. The trial enrolled 123 patients, who had a median baseline viral load of 5.1 log₁₀ c/mL and a median CD4 count of 222 cells/mm³. Fifty-two patients (42%) discontinued therapy prematurely due to adverse events (14), loss to follow-up (13), virologic failure (12), or other reasons (13). Overall, virologic failure occurred in 11% of patients. At 48 weeks, 41% and 75% of patients had viral loads below 50 c/mL by ITT, M=F analysis and ITT observed analysis, respectively. Resistance data from the 14 patients failing therapy were presented by Richard Elion [Abstract H-1068]. At the last study visit on therapy, 5 of 14 patients had wild-type virus, and 9 of 14 had mutations, including TAMs plus M184V in 3, TAMs alone in 3, M184V alone in 1, and K65R in 2. Approximately one-third had phenotypic resistance to study drugs at the last visit.

These results are not a ringing endorsement for this regimen. The high drop-out rate is concerning, as is the resistance profile. Patients failing therapy in the three ACTG 5095 arms, even in the less effective triple-NRTI arm, typically had wild-

type virus, M184V, and/or, in the case of the EFV arms, NNRTI resistance. However, they did not tend to have TAMs or K65R. The presence of these mutations in a sizeable proportion of failing patients raises questions about whether the use of once-daily AZT, clearly a twice-daily drug, might have led to insufficient AZT exposure throughout the dosing cycle, allowing for emergence of AZT-selected TAMs and TDF-selected K65R. Data from trials using the combination of twice daily *Trizivir* plus TDF, while not definitive, have shown more promising results [Moyle G, et al. 44th ICAAC 2004, Washington, DC. Abstract 1131].

Does Viral Suppression Really Matter?

A number of studies have suggested that the short-term prognosis for patients without complete virologic suppression is no worse than for those who maintain viral loads below 50 c/mL. These results have been seized on by those who reject what they refer to as the "dogma of undetectability." However, data from the Danish HIV Cohort Study suggest that viral suppression really does make a difference, including a difference in mortality [Lohse N, et al. Abstract H-515, and *Clin Infect Dis* 2006;42:136-44]. This study looked at virologic control during the first 6-18 months of therapy as a predictor of long-term outcome. The investigators divided the cohort into 3 groups based on the proportion of their viral loads that were detectable (>400 c/mL) during the 6-18 month period after starting HAART: patients in Group 1 never had detectable viremia, those in Group 2 sometimes had detectable viremia (1-99% of the time), and those in Group 3 always had detectable viremia. This was a large study: the analysis included almost 10,000 person-years of follow-up beginning 18 months after initiation of HAART. They found that compared with Group 1, adjusted mortality rate ratios (MRRs) were significantly higher in the groups with detectable viremia: 2.6 in Group 2 and 4.5 in Group 3. Six-year survival was 92.7%, 85.6%, and 76.1%, respectively. In Group 2, treatment interruption was associated with increased mortality (MRR 3.48). In addition, there were significant differences in CD4 cell count increase among the groups, and in rates of virologic suppression after 6 years (96%, 83%, and 57%).



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Of course, such analyses are always subject to selection bias. Patients with detectable viral loads are more likely to be non-adherent, and patients who are non-adherent are more likely to be substance abusers or to suffer from mental illness, conditions that could be associated with increased mortality for reasons that have nothing to do with HIV infection. Nevertheless, these data are some of the strongest to date to suggest that there are clinically relevant consequences to virologic failure.

New Drugs

ICAAC tends to be a very “drug-oriented” conference, and we heard about a number of new antiretroviral agents in Washington.

Darunavir, the new generic name for TMC114, is a second-generation protease inhibitor (PI) from Tibotec that is expected to be the next new antiretroviral agent approved by the FDA. It is now available through an expanded access program. At ICAAC, 24-week data from the POWER-2 trial were presented by Wilkin [Abstract H-413]. POWER-2 is a phase IIb trial in which 278 treatment-experienced patients were randomized to receive one of four doses of ritonavir-boosted darunavir (N=225) or control PIs (N=53) plus an optimized background regimen (OBR). At baseline, the median phenotypic fold-change to lopinavir (LPV) was approximately 80, indicating the extensive treatment experience

among study participants. At 24 weeks, virologic suppression was significantly better with all doses of darunavir than with control PIs, ranging from a 1.2 to a 1.7 log₁₀ c/mL reduction in viral load. By the FDA-mandated intent-to-treat, time to loss of virologic suppression (ITT: TLOVR) analysis, 45-62% of darunavir recipients achieved at least a 1 log reduction in viral load compared to 14% of the control patients. At the highest dose (darunavir/ritonavir 600/100 mg bid), 39% achieved viral load reduction to <50 c/mL compared to 7% of those in the control arm.

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This is in contrast to the results of a similar, concurrent trial, POWER-1, in which 53% and 18% of darunavir and control patients achieved suppression to <50 c/mL, respectively. Patients in the POWER-1 trial had considerably less treatment experience and PI resistance than those in POWER-2, which also helps to explain why use of concomitant use of ENF added less to the overall benefit in POWER-1 than in POWER-2: In the latter trial, 64% of ENF-naïve patients on the 600/100 mg bid dose arm who used ENF in their background regimen achieved viral load reduction to <50 c/mL, compared to 7% of control subjects, and compared to 39% overall for darunavir recipients in the trial. There were no significant differences in adverse events

between the darunavir and control arms, and no clear dose-related toxicities [Berger, et al. Abstract H-1094].

Breacanavir (BCV, HPR10006) is a second-generation protease inhibitor (PI) from GlaxoSmithKline and Vertex that is active against many viral strains exhibiting high-level resistance to currently available PIs. Douglas Ward presented data from an open-label, single-arm study in which 31 treatment-naïve or -experienced patients with CD4 counts over 200 cells/mm³ and viral loads above 1,000 c/mL received a combination of BCV 300 mg bid boosted with ritonavir (RTV) 100 mg bid and two NRTIs [Abstract H-412]. Six of the 31 patients had PI-resistant virus, with a median of two primary PI mutations and 5 secondary mutations. The median phenotypic fold-change to lopinavir (LPV) was 4, with a median fold-change of 1 to BCV. At 24-weeks, 81% and 77% of patients had viral loads below 400 c/mL and 50 c/mL, respectively, by ITT missing=failure analysis. Those with baseline PI resistance experienced a median viral load reduction of 2.2 log₁₀ c/mL. The drug appeared to be well tolerated, with no unexpected adverse events. Larger-scale comparative trials in treatment-experienced patients are now in progress.

Etravirine, an NNRTI, is discussed in my review of the Dublin EACS meeting, also in this issue, but under its previous name, TMC125. Howard Grossman presented data from the TMC125-C223 trial [Abstract H-416c]. This study was also presented in Dublin, and the study design is described in the EACS review. In the ICAAC presentation, 21% and 18% of patients on the etravirine 400 and 800 mg bid arms achieved viral load suppression to <50 c/mL at week 24 by ITT analysis, compared to 7.5% of those in the control arm. CD4 increases were 47, 48, and 10 cells/mm³, respectively. When ENF-naïve patients who used ENF in the background regimen were analyzed, there was a significant difference favoring both etravirine arms. The time to discontinuation was significantly shorter in the control arm: three-quarters discontinued therapy due to virologic failure. Rash occurred in 20% of etravirine recipients compared to 8% of control patients, and rash was felt to be at least possibly drug-related in 15%. The median time to onset of rash was

13 days, and median duration was 5 days. There was no clear association with CD4 count. Five patients (3%) discontinued therapy due to rash.

PA-457, being developed by Panacos, is the first “maturation inhibitor”; it targets the gag gene to block cleavage of CA-SP1, a precursor of the HIV capsid protein. Results of a dose-ranging, 10-day monotherapy trial of PA-457 vs. placebo were presented at ICAAC [Beatty G, et al. Abstract H-416d]. Participants taking 50, 100, or 200 mg/day of PA-457 had significantly greater viral load reduction at 10 days compared to patients in the placebo arm (-0.17, -0.48, and -1.03 vs. +0.03 log₁₀ c/mL, respectively). The drug was well tolerated at all doses.

TNX-355 is an anti-CD4 monoclonal antibody from Tanox that selectively blocks attachment of HIV gp120 to the CD4 receptor. It is given by an intravenous infusion every 1-2 weeks. Norris presented data from a clinical trial comparing TNX-355 plus OBR vs. OBR alone in treatment-experienced patients [Abstract 4020]. Patients who received the highest dose, 10 mg/kg/wk, had a viral load reduction of 1.16 log₁₀ c/mL at 24 weeks, compared to 0.2 log for control patients (p<0.001). Twenty-two percent achieved a viral load <400 c/mL, compared to 0% in the control arm. The drug was well tolerated, and in a separate presentation by Elliot Godofsky, the drug showed activity against R5-, X4-, and dual/mixed tropic viruses, and demonstrated evidence of synergy with ENF [Abstract 3844]. ▲

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The 10th European AIDS Conference (EACS) was held in Dublin from November 17-20, immediately following the Lipodystrophy Conference, reported on in this issue by Joseph Confrancesco and Todd Brown. Dublin has become a sophisticated, cosmopolitan, international (and expensive!) city without losing its charm. (And it's true what they say...the Guinness really does taste better in Ireland!)

Treatment-Naïve Patients

The Nuke-Sparing Strategy Takes Another Hit

The Hippocampe study (ANRS 121) compared NRTI-sparing vs. NRTI-containing regimens in treatment naïve patients with CD4 counts <350 cells/mm³ or viral loads >100,000 c/mL [Duvivier C, et al. Abstract PS1/3]. The protocol allowed use of any NRTI except d4T and ddC; NNRTIs allowed were nevirapine (NVP) and efavirenz (EFV); PIs were ritonavir-boosted indinavir (IDV/r) and lopinavir (LPV/r). The original aim of the study had been to compare metabolic and morphologic toxicity between the arms, but the study was terminated early after an analysis of 36-week data by the DSMB showed a significant difference favoring the NRTI-based regimens by both intent-to-treat and on-treatment analyses. NRTI-sparing regimens had lower rates of virologic success and slower rates of viral load decline. In addition, the only resistance mutations observed were in those patients failing NRTI-sparing regimens.

These results are consistent with those of ACTG 5116, in which the combination of EFV + 2 NRTIs was superior to an NRTI-sparing regimen of EFV + LPV/r, in part because of a greater discontinuation due to drug toxicity in the NRTI-sparing arm [Fischl M, et al. 12th CROI, Boston, 2005. Abstract 162]. Enthusiasm for NRTI-sparing regimens has waned in recent years, in part because of the disappointing results of these trials, and in part because of the improved tolerability, toxicity, and convenience of the newer NRTI backbones. Nevertheless, it should be noted that the problems with the NRTI-sparing regimens that have been tested to date are at least partly due to toxicity and tolerability issues that may not apply to all such regimens. For example, the combination of EFV + LPV/r

has so far required use of the soft-gel capsule formulation of LPV/r, with an increased dose of LPV/r (4 caps bid) because of the interaction with EFV. Combinations of EFV with atazanavir/ritonavir (ATV/r), fosamprenavir/ritonavir (FPV/r), or the new tablet formulation of LPV/r might be better tolerated.

Options for Patients with Advanced Disease: Busting the PI Mythology

Some clinicians still cling to the dogma that patients with high viral loads or low CD4 cell counts at baseline need a PI-based regimen, though this dogma has never been supported by data. Jose Miro from Barcelona presented results from a 2-year, randomized, multicenter, open-label trial comparing NNRTI- vs. PI-based regimens as initial therapy in 60 patients with CD4 counts <100 cells/mm³ (mean baseline CD4 count 40 cells/mm³) [Abstract PS1/4]. At 2 years, there was no difference in virologic suppression by intent-to-treat or on-treatment analysis, and there was no difference in rate of disease progression or death. Immune response was at least as robust in the NNRTI arm as in the PI arm: CD4 increase was 271 vs 222 cells/mm³, respectively (P=NS), and the percentage of patients with CD4 counts >200 cells/mm³ was 94% vs 80% (P=NS). Increases in naïve and memory CD4 cells were also the same. CD8+CD38+, a marker of immune activation, decreased in both arms, but the decrease was greater in the NNRTI arm. NNRTI-based regimens were better tolerated: only 12% discontinued due to adverse events, vs. 32% in the PI arm

This study is limited by its small sample size and by the choice of PIs. Those in the NNRTI arm took EFV, with NVP as a back-up for those who could not take EFV. However, the PI of choice was IDV/r (800/200 mg bid), with LPV/r as a back-up. Boosted IDV is infrequently used today because of its toxicity, which may have been further increased by use of a 200 mg boosting dose of RTV. Nevertheless, the results of this trial are consistent with those of a number of other studies that suggest that NNRTI-based regimens, especially EFV-based regimens, can be appropriate choices for patients with advanced disease. We are eagerly awaiting the results of what may be the definitive study: an ongoing ACTG trial comparing LPV/r + 2 NRTIs,

EFV + 2 NRTIs, and LPV/r + EFV in treatment-naïve patients.

Treatment-Experienced Patients

Tipranavir: 48-week RESIST Results

Pedro Cahn presented the 48-week pooled analysis of two tipranavir (TPV) trials, RESIST-1 and RESIST-2 [Abstract LBPS3/8]. Earlier results from these trials have been previously reported and discussed [Lucas G, *HHR* 2005;17(2):1 and Lucas G *HHR* 2005;17(5):4]. A total of 1,509 patients with extensive triple-class treatment experience were randomized to take TPV/r vs. a comparator boosted PI (CPI/r). Patients had to have PI mutations, but could not have more than 2 of the mutations that were thought at that time to be most predictive of TPV resistance: protease mutations at codons 33, 82, 84, and 90. Virologic response was superior in the TPV/r arm, and that superiority was maintained over the 48-week study period. A viral load reduction of over 1 log₁₀ c/mL was observed in 34% of those on TPV/r vs. 15% of those in the CPI/r group. Viral load decline was 1.14 and 0.54 log₁₀ c/mL, respectively. Suppression to <50 c/mL was observed in 23% and 10%, respectively. The best response was seen in TPV/r-treated patients who were previously enfuvirtide (ENF)-naïve and who used ENF in their background regimen: 35% achieved viral suppression to <50 c/mL vs. 14% in ENF-treated patients on the CPI arm. As has been reported in earlier presentations of these trials, TPV/r-treated patients were more likely to have grade 3 or 4 elevations in ALT, AST, cholesterol, or triglycerides than patients in the control arm.

Lopinavir/ritonavir Monotherapy Studies

The possibility of treating patients using monotherapy with a boosted PI has been best studied using LPV/r, and we heard more data in Dublin from ongoing monotherapy trials. Pulido presented week 72 data from the OK ("Only Kaletra") study, in which 42 patients with no prior history of PI failure who were doing well (viral load <50 c/mL for >6 months) on a combination of LPV/r + 2 NRTIs were

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randomized to continue their current regimen or to switch to LPV/r monotherapy [Abstract #PS7.5/5]. At 72 weeks, virologic suppression to <50 c/mL by ITT, missing = failure analysis was achieved in 90.5% of those on LPV/r + 2 NRTIs and 81% of those on LPV/r monotherapy. Two patients in the former group discontinued due to hyperlipidemia, whereas in the monotherapy arm there was one loss to follow-up and 3 virologic rebounds. Among those who experienced rebound, there was no evidence of new resistance, and all patients resuppressed with addition of NRTIs. The best predictor of virologic rebound was suboptimal adherence as determined by medication refill records.

In the KalMo study, 60 patients who maintained virologic suppression for over 6 months on HAART were randomized to continue their current regimen or to switch to LPV/r monotherapy [Nunez EP, et al. Abstract PE 7.5.1]. Data were available on 51 patients who had completed 24 weeks of therapy. No patient experienced overt virologic failure (viral load >1000 c/mL), although there were two low-level rebounds (viral load 410 and 470 c/mL) on the LPV/r arm. One patient in the monotherapy arm and two in the standard HAART arm discontinued therapy due to adverse events.

The accumulating data on LPV/r monotherapy are promising, and suggest that this is a strategy worthy of further study. However, in each trial, there have been patients who have experienced virologic rebound, often for unclear reasons. Fortunately, no participant has developed PI resistance to date, and resuppression is achieved with addition of NRTIs. These observations raise the question of whether there are anatomical or pharmacologic compartment issues that prevent this approach from working in 100% of patients.

Antiretroviral Strategies

SWAN: Switching to Atazanavir

José Gatell from Barcelona presented final, 48-week results from the SWAN study, an open-label, randomized trial in which 490 patients who were virologically suppressed on a PI-based regimen without a prior history of PI failure were randomized in a 2:1 fashion to switch to an ATV-based regimen or to continue their current PI

[Abstract PS1/1]. ATV was unboosted except in the case of patients on tenofovir DF (TDF)-containing regimens, who represented approximately 10% of the participants. By intent-to-treat analysis, virologic rebound to >50 c/mL was more common among those who remained on their original PI-based regimen (16%) compared to those who switched to ATV (7%, $p < 0.01$). Treatment failure for any reason occurred in 21% of those randomized to switch to ATV vs. 34% of those who remained on the original regimen ($p < 0.01$). Although more participants in the original PI arm dropped out of the study following randomization, the differences between arms persisted when the analysis was restricted to the patients who were treated with the assigned regimen. Rates of discontinuation due to adverse events were the same in the two arms. Not surprisingly, jaundice or scleral icterus occurred only in the ATV arm (11%), while diarrhea and hyperlipidemia were more common in the original PI arm. There were no differences in transaminase elevations, including in patients with chronic hepatitis C.

It is worth noting that only 54% of the participants were on a ritonavir-boosted PI at baseline. When the data were analyzed based on boosting of the original PI regimen, the differences between the arms were significant only among those taking an unboosted PI-based regimen, most of whom were on nelfinavir or indinavir. In this subset analysis, virologic failure occurred in 5% of the ATV arm vs. 22% of the comparison arm ($p > 0.001$). Overall, these results suggest that ATV is well tolerated with respect to gastrointestinal side effects and is less likely to cause hyperlipidemia than other PIs. It is associated with better efficacy than other unboosted PIs, but not necessarily compared to boosted PIs.

Blips: Still Common, Still Benign

Gaia Nebbia presented data on blips among patients on stable HAART for at least six months with virologic suppression to <50 c/mL [Abstract PS3/5]. Of 486 patients, 119 (24.%) experienced blips, of whom 70% had a single blip. There was no difference in the rate of virologic failure between “blippers” and “non-blippers,” and those who blipped did not experience the emergence of new resistance mutations.

These results are consistent with those of other studies, including Richard Nettles' study from Hopkins, which found that blips were common and not associated with emergence of new resistance mutations [JAMA 2005;293:817-29]. However, while the findings are reassuring, blips continue to pose a challenge to clinician managing patients in “real time.” A patient with a newly detectable viral load may be simply “blipping,” but he may also be experiencing early virologic failure. Unfortunately, there is no way to be sure without repeating the viral load.

New Agents

TMC125

Julio Montaner presented a 24-week analysis from TMC125-C203, a phase II double-blind, placebo-controlled, dose-escalation trial in which 240 triple-class experienced patients with viral loads >1,000 c/mL received an optimized background regimen plus either placebo or one of two doses (400 or 800 mg bid) of TMC125, the investigational NNRTI from Tibotec [Abstract LBPS3/7B]. After a DSMB review of 24-week data, doses were increased to 800 and 1,200 mg bid. The study required use of at least two active drugs in the optimized background regimen, which may explain why efficacy differences were not observed. The focus of Montaner's presentation was on toxicity. In comparison to the placebo arm, there did not appear to be significant differences between TMC125 recipients and those on placebo with respect to diarrhea, headache, nausea, abdominal pain, fatigue, or any grade 3 or 4 adverse events or serious adverse events. There were no clear dose-related side effects. Mild-to-moderate rash was seen in 17% of those in the combined TMC125 arms vs. 11% in those on placebo. There was no relationship between rash and TMC125 dose, CD4 count, or gender. Median time to onset of rash was 13 days. There were also no consistent or frequent neuropsychiatric side effects.

Jeffrey Nadler presented 24-week efficacy and tolerability data from TMC125-C223, in which patients failing therapy with NNRTI resistance and at least 3 primary PI mutations were randomized in a 2:2:1 fashion to receive 400 mg bid (N=80) or 800 mg bid (N=79) of TMC125



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or control (N=40) [Abstract LBPS3/7A]. Over 90% of participants had virus that was resistant to all licensed PIs, and the majority had at least 2 NNRTI mutations. At 24 weeks overall viral load change by ITT, non-completer=failure analysis was -1.04 and -1.18 log₁₀ c/mL in the 400 and 800 mg arms, respectively, vs. -0.19 in the control arm. When the analysis was confined to those whose background regimen included at least 2 drugs to which the patient's virus was susceptible, viral load decline was considerably higher: -1.66, -1.49, and -0.49 log₁₀ c/mL, respectively. CD4 cell count increase was also higher and time to discontinuation of therapy longer in the TMC125-treated patients. The 800 mg bid dose was chosen for further development. However, a new formulation has now been developed that allows a dose of 200 mg bid (4 pills/day) which provides comparable exposure to 800 mg bid of the original formulation.

Unfortunately, another TMC125 study (C227) was recently discontinued based on review of preliminary results by the DSMB. This was an open-label, phase II study in PI-naïve patients failing a first-line NNRTI-containing regimen, who were randomized to receive TMC125 vs. a PI plus 2 NRTIs. After evaluation of the first 54 patients reaching 12 weeks, it was clear that the proportion of patients achieving or maintaining a viral load <50 c/mL was lower in the TMC125 arm than in the PI arm. The sponsors noted that this study was being conducted with the old formulation of TMC125, which is more dependent on food for bioavailability. It is also worth pointing out that the background regimen could include only 2 NRTIs, despite the fact that all patients had previously failed an NRTI-containing regimen, and had presumably developed some degree of NRTI resistance (at least M184V). The other trials involving TMC125, which use the newer formulation, are ongoing.

MK-0518: Merck's Integrase Inhibitor

Results of a 10-day, dose-ranging, monotherapy trial of MK-0518, Merck's investigational integrase inhibitor, were presented by Morales-Ramirez [Abstract LBPS1/6]. The trial was conducted in 35 HIV-infected, treatment naïve patients, who were assigned to take MK-0518 at doses of 100, 200, 400, or 600 mg twice

daily vs. placebo. Viral load response in the MK-0518-treated patients was 1.7-2.2 log₁₀ c/mL at ten days, with no obvious differences among doses. There were no grade 3 or 4 laboratory abnormalities, no serious adverse events, and no discontinuations due to adverse events. A larger study comparing MK-0518 with efavirenz is in progress.

CCR5 Inhibitor Troubles

Development of aplaviroc, the GlaxoSmithKline candidate, has been abandoned because of significant liver toxicity. Five cases of liver toxicity have now been reported in patients treated with aplaviroc in clinical trials, affecting both treatment-naïve and experienced patients [Nichols WG, et al. Abstract #LBPS5]. The pattern of toxicity included increases in both hepatic transaminases and total bilirubin, an uncommon pattern of drug toxicity that has been associated with a high risk of liver failure or death.

Meanwhile, a study involving vicriviroc, the Schering-Plough agent, has been stopped [Fatkenheuer G, et al. Abstract PL6]. The trial compared vicriviroc with efavirenz in treatment-naïve patients, always a tough battle. Patients in the vicriviroc arm had lower rates of virologic suppression than those on efavirenz. It has been suggested that the differences may have been due to excessively low doses of vicriviroc, as there appeared to be a dose-response relationship in this trial involving 3 doses of vicriviroc.

The Pfizer compound, maraviroc, is still being studied in both naïve and experienced patients. A case of serious liver toxicity requiring transplantation was reported via press release and discussed in Dublin, but the relationship of the hepatotoxicity and maraviroc is unclear, since the patient had many other reasons for developing liver problems, including use of other hepatotoxic agents such as isoniazid, trimethoprim/sulfamethoxazole, LPV/r, and intravenous acetaminophen, the latter having been given *after* the development of hepatitis. The DSMB felt that the patient probably had hepatotoxicity due to other agents, but could not rule out the possibility that it was related to maraviroc. They recommended that ongoing phase 2b/3 trials be continued. ▲

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Report From the International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

By Joseph Cofrancesco, Jr., M.D., M.P.H. and Todd Brown, M.D.

The 7th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, held in Dublin on November 13-16, 2005, was a productive meeting, providing further insights into the complications of HIV treatment. A number of well conducted basic science and clinical studies were presented that may lead to improved treatment options for HIV-infected patients. The following is a report on the more clinically relevant abstracts.

Fat Loss and Fat Gain Not Linked

HIV fat changes were first described as “fat redistribution,” with the assumption that the peripheral fat loss and central fat gain was linked and reciprocal. Many studies made this assumption in their methodology, and the term “lipodystrophy” was used for all fat changes. Some researchers still refer to HARS (HIV-associated redistribution syndrome). However, it has become increasingly clear that fat loss and fat gain are two distinct phenomena with different risk factors. Andrew Carr’s group reviewed data from all participants in the MITOX study, 98% of whom were male, which evaluated the effect of switching from stavudine (d4T) or zidovudine (AZT) to abacavir (ABC), and the ROSEY study, which found no effect of rosiglitazone on peripheral fat compared to placebo [Wand H, et al., Abstract 3]. The authors found that an increase in limb fat in men recovering from lipoatrophy was associated with an increase in subcutaneous abdominal fat as well as a modest increase rather than a reduction in visceral fat. Additionally, they found that risk factors were different for improvement in lipoatrophy (higher baseline body mass index) vs. decrease in visceral fat (higher limb fat mass, lower HDL cholesterol, higher insulin level, greater limb fat decreases). This suggests these fat changes are separate processes, and supports the newly emerging literature, especially the recently published FRAM study [Bacchetti P, et al. *J Acquir Immune Defic Syndr.* 2005;40(2):121]. Providers and researchers should look at fat loss and fat gain separately, and should avoid lumping them together with imprecise terms such as “fat redistribution” or “lipodystrophy.”

Nutritional Supplements

A number of small studies looked at use of nutritional supplements and body composition. Sakkas reported on a study of 33 HIV-infected men randomized to receive creatine monohydrate (loading dose of 20g/day for 5 days, then 4.8 g/day in repeated 6 week cycles) or placebo [Abstract 6]. After the first 2 weeks of the study, all subjects, with the exception of 7 who dropped out, underwent 12 weeks of supervised resistance training three times a week. Resistance training improved muscle size and strength; creatine increased lean body mass but did not increase strength. The implication is that we should not be recommending creatine to enhance muscle growth in our HIV-infected men, particularly since there is always doubt about the purity of supplements, and the potential toxicities are unclear. This study did report small increases in serum creatinine and triglycerides (TG) with the supplement. These results do emphasize that resistance training is a valuable way for people with HIV to maintain and build muscle and strength.

Uridine is the ‘hot’ compound for treating lipoatrophy. This supplement is purported to assist in recovery from mitochondrial damage, and preliminary results show promise. Sutinen reported on a study from Finland in which 20 men with lipoatrophy on either d4T or AZT were randomized to take the uridine-rich dietary supplement NucleomaxX (36 g tid for 10 days/month) or placebo for 3 months [Abstract 7]. The average increase in total limb fat by DXA for those receiving uridine was 21% compared to 7% in the placebo group. Intra-abdominal fat measured by MRI also increased significantly over the study period. There was no change in liver fat. This preliminary study suggests that this compound may be useful in helping those with lipoatrophy regain some lost fat. NucleomaxX was also associated with improvements in fat and blood mitochondrial DNA [McComsey G, et al. Poster 82]. However, this study had a very small number of subjects. Additionally, NucleomaxX is not widely available, tastes bad, and is quite expensive. It may be that uridine will have better utility for the

prevention of lipoatrophy rather than for recovery of lost fat. For clinicians in the US, it seems more reasonable to avoid medications toxic to mitochondria (especially d4T and AZT) than to add a supplement. An ACTG trial of uridine is planned.

Increases in Limb Fat With Lipid-Lowering Therapy

Quite unexpectedly, pravastatin was shown to increase limb fat by both DXA and computed tomography (CT) in a randomized, placebo-controlled study of 33 HIV-infected patients with hypercholesterolemia [Mallon PWG, et al. Abstract 23]. Despite a negligible effect on lipid parameters, the study’s primary endpoint, limb fat increased by an average 0.72 grams over 16 weeks in those randomized to pravastatin (40 mg qhs) compared to a non-significant 0.19 g increase in the placebo group. To put these results in perspective, this increase in limb fat was more than double what was seen after d4T discontinuation in the MITOX study. Further research is needed to confirm these findings and elucidate the underlying mechanism before it can be embraced by the clinical community.

Switch Studies

Continuing the theme that switching from medications that are associated with facial lipoatrophy is a viable option, Benn presented further data on the previously published RAVE study, which randomized patients to switch from d4T or AZT to ABC or TDF in a 1:1 randomized fashion [Abstract 8]. This substudy focused on 47 subjects and compared limb fat DXA measurements with 3D facial laser imaging at baseline and week 48. The authors found that switching was associated with improvements in facial volume similar to that seen with collagen injections, with no differences between ABC and TDF. Cheek volume changes correlated with limb fat changes. This study supports switching from a thymidine analog to either ABC or TDF, with no apparent difference between the two, for patients with lipoatrophy who can safely make such a switch.

Given the association of facial and limb fat, we may be able to extrapolate limb fat



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changes from other lipoatrophy switch and treatment studies to facial fat. In addition, a number of posters reported on improvement in lipids and other metabolic parameters when changing from d4T to TDF [da Silva B, et al. Abstract 62; Libre JM, et al. Abstract 63; Zhong L, et al. Abstract 64]. Taken together, there is more than sufficient evidence that nucleoside analogs, especially d4T and to a lesser degree AZT, are associated with lipoatrophy, insulin resistance, and dyslipidemia, and that alternative NRTIs may be preferred, at least for initial therapy when patients have many options.

Lipids

Treatment of lipid abnormalities was also an important topic at this meeting. Michael Dubé reported on ACTG 5148, a 48-week, multicenter, open-label, prospective trial of extended release niacin in subjects with TG >200 mg/dL, but non-HDL cholesterol <180 mg/dL, and LDL cholesterol <130 mg/dL [Abstract 12]. Patients received nutritional advice for the first 4 weeks (step 1), then niacin was titrated up to 2000 mg/day based on pre-established TG levels. The study participants were all male, with 61% white, 18% black, and 12% Hispanic. The authors found that extended-release niacin in doses of up to 2,000 mg/day, given with aspirin beforehand, was well tolerated and decreased TG by an average of 38%. HDL cholesterol increased by 15%, although LDL particle size and quantity did not change. Subtle changes seen in glucose metabolism at week 12 generally returned to baseline by week 48, although fasting insulin levels remained minimally elevated. These findings suggest a role for niacin in patients with a low HDL and a high TG. However, patients with high LDL cholesterol were excluded from this study, so it will be important to test this agent in combination with a statin and to further evaluate its effect on insulin resistance.

Insulin Resistance

Carl Grunfeld reported that a single dose of 1200 mg of amprenavir given to 6 healthy, male, HIV-infected volunteers in a double-blind, cross-over study did not decrease insulin-mediated glucose disposal ascertained by the euglycemic hyper-

insulinemic clamp technique [Lee GA, et al. Abstract 15]. This study should not be over-interpreted, however, as what happens over time in HIV-infected patients is far more complicated, and insulin resistance is likely to be due to a combination of effects. However, the authors had previously reported that a single dose of indinavir (IDV) did induce insulin resistance, [Noor MA, et al. *AIDS* 2002;16 (5):F1-8] and IDV has clearly been associated with insulin resistance clinically. The group plans on expanding these very labor- and time-intensive experiments in healthy volunteers with other, newer PIs, as well as PIs boosted with low dose ritonavir.

Mustafa Noor from Bristol-Myers Squibb reported a randomized, cross-over study comparing atazanavir/ritonavir (ATV/r) (300/100 mg qd) and lopinavir/ritonavir (LPV/r) (400/100 bid) given for 10 days to 24 healthy, HIV-negative subjects [Abstract 16]. Treatment with ATV/r did not alter insulin sensitivity using the clamp technique, although TG did increase from 108 mg/dL at baseline to 140 mg/dL, with a small increase in insulin area-under-the-curve (AUC) during the oral GTT, another measure of insulin resistance. In contrast LPV/r was associated with significant decreases in insulin sensitivity, larger increases in insulin AUC, and greater increases in TG (to 161 mg/dL).

Bristol-Myers Squibb reported on *in vitro* experiments studying insulin secretion in murine pancreatic beta-cells stimulated by glucose with or without amino acid co-stimulation in the presence of various PIs [Flint OR, et al. Abstract 50]. In this study the relative inhibition by protease inhibitors was RTV=LPV>IDV>ATV (the latter with very little inhibition). Taken together, these studies should remind providers that not all PIs have the same metabolic toxicities. Although there are PI class effects on insulin sensitivity, the magnitude of the effect varies considerably. Here, as with other studies, APV and ATV, even when boosted, appear to be less toxic than LPV/r.

Finally, Diop and colleagues compared actual blood glucose levels with those estimated by hemoglobin A1c (H A1c) six weeks later in HIV-infected and non-infected patients [Diop M-E, et al Abstract 5]. They found that in HIV-infected patients H A1c underestimated glucose

levels by an average of 12.3%. The authors suggest that this discrepancy is due to low-grade hemolysis induced by lamivudine, but further work is needed to clarify this mechanism. Nonetheless, clinicians should be aware of the possibility that use of H A1c may underestimate control of diabetes in HIV-infected patients.

Clinicians and patients in resource-rich nations continue to learn more about the science of metabolic toxicities, and are able to select treatment to avoid or treat toxicities. However, there is concern that patients in resource-limited countries, who have limited access to newer drugs, will inevitably experience many of these toxicities.

Summary

At this year's meeting data were presented further reinforcing the concept that changes in subcutaneous fat and visceral fat are two different processes with different risk factors. New analyses of existing studies continue to show higher rates of limb fat loss with d4T, and to a lesser degree with AZT, compared to other NRTIs. In addition, data were presented that continue to demonstrate the benefit of switching from thymidine analogs to ABC or TDF as treatment for lipoatrophy. An interesting study suggested that pravastatin increased limb fat; this gain appeared to be greater than that accomplished with a switch from d4T to another NRTI. Several studies of nutritional supplements were presented. Supplementation with creatine resulted in increased lean body mass, but considering the possibility of impure commercially available products and unknown toxicities, it cannot be recommended. Uridine appeared to be beneficial in countering fat loss, but the commercially available supplements are expensive, difficult to find, and unpalatable. Niacin was shown to be beneficial in reducing TG and increasing HDL. Finally, several studies continue to show the propensity of PIs to induce metabolic toxicities, while emphasizing the differences among the individual PIs. ▲



USPHS Updates Occupational HIV Post-Exposure Prophylaxis Guidelines

By John G. Bartlett, M.D.

On September 30, 2005 the U.S. Public Health Service released its Updated Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis (PEP) [MMWR *Recomm and Rep* 2005; 54(RR-9):1]. This is the first “official” update in these guidelines since June 2001 and reflects additional drugs available for PEP as well as additional information about the use and safety of PEP for HIV prevention.

Risk for HIV Transmission

The risk of transmission continues to be related to exposure to infectious material and the source of that material. Exposure is defined as either percutaneous injury with a contaminated sharp object or exposure of mucous membranes or non-intact skin (skin that is abraded, chapped or with dermatitis) to infectious material. The current understanding of exposure contingencies is summarized in Table 1.

The risk of HIV transmission (without prophylaxis) is 0.3% (3/1000) from percutaneous injury and 0.09% (9/10,000) from mucocutaneous exposure. The following are associated with increased risk of transmission: device (needle) with visible blood, needle used in artery or vein of source patient, deep injury, large volume, high viral load.

Efficacy of PEP

The efficacy of zidovudine monotherapy prophylaxis is estimated to be 80% based on the results of a retrospective case-control study. To date there have been only six recorded prophylaxis failures in the US associated with occupational exposures.

Management of Health Care Workers (HCW) With Potential HIV Exposure

The importance of rapid action in the event of a potential exposure cannot be over-emphasized, since PEP, if warranted, needs to be initiated within hours.

Table 1: HIV Exposure Contingencies

Exposure Element	Explanation
Material	
Blood or bloody body fluid	Established risk of transmission with occupational exposure
CSF; pleural, pericardial, peritoneal, amniotic and vaginal fluids; semen	Theoretical risk of transmission
Urine, stool, nasal secretions, sputum, tears, vomitus (if not bloody)	Not potentially infectious
Type of Exposure	
Percutaneous: Not Severe More severe	Solid needle or superficial injury etc. Large bore hollow needle, deep injury or visible blood on needle/device
Mucocutaneous: Small volume Large volume	Few drops Major splash
Source Infectiousness	
HIV positive Low risk	HIV positive and asymptomatic, viral load <1500 c/mL
High risk	HIV positive and symptomatic, AIDS, acute retroviral syndrome, or known high viral load
Source unknown	For example, deceased source person with no samples available for HIV testing.

Table 2: Determination of Need for HIV PEP

Source	Type of Exposure			
	Percutaneous		Mucocutaneous	
	Not Severe*	More severe*	Small volume*	Large volume*
HIV positive				
Low risk*†	2 drugs	≥3 drugs	2 drugs	2 drugs
High risk*†	3 drugs	≥3 drugs	≥3 drugs	≥3 drugs
Source unknown				
–	None or 2 drugs‡	None or 2 drugs‡	None or 2 drugs‡	None or 2 drugs‡

* See Table 1 for explanation

†If HIV resistance is a concern, seek expert consultation

‡PEP is optional based on discussion of risk:benefit

Table 3. Current Recommended PEP Regimens

2 Drug Regimen	3 Drug Regimen
Lamivudine or emtricitabine <i>plus</i> zidovudine, stavudine or tenofovir	Two nucleosides (see 1st column) <i>plus</i> Preferred: lopinavir/ritonavir Alternatives: atazanavir, fosamprenavir, ritonavir-boosted indinavir, ritonavir-boosted saquinavir, or nelfinavir*



USPHS Updates Occupational HIV Post-Exposure Prophylaxis Guidelines

Assessment

Documentation of the nature and degree of the exposure and the HIV status of the source patient is critical. Rapid testing of previously untested source patients is valuable in determining the need for PEP. The need for PEP and potential number of drugs may be determined by using Table 2 on p 10.

Initiation of HIV PEP

Initiate PEP as soon as possible, preferably within hours after exposure, and continue for 4 weeks. From a practical point-of-view, PEP should be initiated if the source is HIV-infected or thought to be infected, especially if the results of HIV serology are likely to be delayed; PEP may be discontinued if the source is later determined to be uninfected. The current recommended PEP regimens are listed in Table 3 on p 10.

The following drugs are not recommended because of the potential for adverse events: abacavir, delavirdine, zalcitabine, didanosine with stavudine, and nevirapine. During pregnancy avoid efavirenz because of the risk of teratogenic effects and avoid the combination didanosine with stavudine because of toxicity concerns. Additionally, indinavir should be avoided because of the potential for side effects in the newborn.

Health care workers taking PEP report adverse reactions at the rate of 17% to 47%. The most frequently reported reactions were nausea– 27%, malaise and fatigue– 23%. Of 503 HCW who prematurely (<28 days) stopped PEP 24% did so because of adverse reactions. Regardless, the HCW should be advised on the need to complete the 4-week course of PEP. These data came from HCWs who primarily took zidovudine-containing regimens. The new guidelines now include alternatives to zidovudine, which may be better tolerated.

Expert Consultation

Consultation with an expert in HIV exposures and PEP is encouraged especially in the following instances:

- Initiation of PEP is delayed to >24-36 hrs post-exposure
- The status of the source patient is unknown
- The HCW is currently pregnant or is breastfeeding
- The source patient is known to have a resistant HIV strain
- There are toxicity problems in the initiated regimen

Monitoring

- Re-evaluate HCW at 72 hours, especially if additional information becomes available about the status of the source.
- HIV serologic testing should be conducted at baseline, and then at 6 weeks, 12 weeks and 6 months after exposure. If the HCW experiences hepatitis C seroconversion after exposure, then HIV serology should be repeated 12 months after exposure.
- Tests for HIV (p24 Ag or HIV PCR) in HCW are not

routinely recommended due to potential for false positive results; these tests are indicated if there are symptoms compatible with the acute retroviral syndrome.

- Toxicity monitoring.

Laboratory

CBC, liver and renal function tests at baseline and at 2 weeks. HCWs given protease inhibitors should also have a blood glucose at baseline and 2 weeks. HCWs given indinavir should also have urinalysis, monitoring for crystalluria and hematuria.

Self Report

HCWs should be advised to report rash, fever, back or abdominal pain, dysuria, blood in urine, and symptoms of hyperglycemia. They should also be counseled on the possibility of drug interactions and advised to report these should they occur.

Prevention Warnings

HCWs with exposure to HIV should be counseled on measures to prevent secondary transmission, especially in the first 6-12 weeks post-exposure, including avoidance of blood or tissue donations, avoidance of pregnancy and breastfeeding, and use of condoms to prevent sexual transmission.

Seroconversions

Report any seroconversion to CDC at 1-800-893-0485

Resources

The following resources are available for consultation regarding HIV PEP:

PEPline

<http://www.ucsf.edu/hivcntr/Hotlines/PEPline>
Telephone: 1-888-448-4911

HIV Pregnancy Registry

<http://www.apregistry.com/index.htm>
Telephone: 1-800-258-4263
Email – registry@nc.crl.com

FDA (for reporting unusual or severe toxicity to antiretroviral agents)

<http://www.fda.gov/medwatch>
Telephone: 800-332-1088

CDC (for reporting HIV infections in HCP and failures of PEP)

Telephone: 800-893-0485
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<http://aidsinfo.nih.gov>

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