

THE HOPKINS HIV REPORT

A bimonthly newsletter for health care providers

 Report from Seattle (Continued): The 9th Conference on Retroviruses and Opportunistic Infections (CROI)

Update on Women and HIV

By Jean Keller, PA-C, Brenda Ross, M.D., and Jean R. Anderson, M.D.

Although new information presented about issues relevant to reproductive health and pregnancy in HIV-infected women was sparse at the 9th CROI, there were a few key presentations and a number that add important emphasis to previous observations.

Genital Tract HIV

Several presentations addressed factors related to cervicovaginal shedding of HIV, which likely plays an important role in the infectiousness of persons with HIV. Critchlow presented data on 170 women infected with HIV-1 and 51 with HIV-2, comparing plasma and vaginal RNA and DNA viral loads [Abstract 19]. Frequency of detection of vaginal HIV RNA was higher among women infected with HIV-1 compared with HIV-2 (82% vs 59%). Vaginal HIV RNA was highly correlated with plasma HIV RNA. Vaginal HIV RNA could be found in the absence of HIV DNA: HIV-1 RNA was detected in 73% of samples with negative HIV-1 DNA and in 53% of HIV-2 DNA negative samples. Local factors associated with vaginal HIV RNA in both groups included elevated vaginal pH and genital tract infections, including bacterial vaginosis, trichomoniasis, HPV, and candidiasis.

In a prospective study of 19 HIV-1 infected and 11 HIV-2 infected Senegalese women followed for up to 6 weeks, vaginal lavage specimens were collected every 3 days [Hawes, Abstract 785-W]. In multivariate analysis after adjusting for plasma HIV RNA, detection of genital HIV was associated with HIV-1 infection (OR=3.2), recent menses (OR=3.2), amenorrhea

(OR=6.5), and low CD4 count (OR=5.4 for CD4 <200/mm³). Over a six-week period, 87% of women infected with either HIV-1 or HIV-2 had detectable levels of HIV in vaginal lavage specimens at some time, even in the presence of low plasma HIV RNA levels. However, virus was only detected intermittently in 47% of women.

Cu-Uvin compared two different collection methods to assess HIV in the genital tract. Among 78 women with paired cervicovaginal lavage (CVL) and *Sno-Strip* cervical samples, *Sno-Strip* cervical samples clearly outperformed CVL [Abstract 782-W]. Forty percent of *Sno-Strip* samples had HIV RNA levels greater than plasma viral load, compared with only 7.5% of CVL samples (p<0.001). The *Sno-Strip* collection technique detected HIV RNA in 22% of samples when CVL was undetectable (<400 c/mL). The findings are thought to be due to the dilutional effect of CVL and/or viral load differences within various genital compartments (the endocervix may be the primary source of HIV in the female genital tract).

Pregnancy and hormonal contraceptive use have been correlated with cervicovaginal shedding of HIV-1 in past studies. Two studies presented at the 9th CROI evaluated additional factors associated with HIV-1 RNA in genital secretions. The relationship between the menstrual cycle and daily genital HIV-1 RNA shedding was examined in a study of 17 women over 1 month and included measurement of luteinizing hormone (LH), estrogen and progesterone throughout the cycle, as well as plasma viral load [Benki, Abstract LB2]. There was an increase of 0.05 log₁₀ HIV

RNA c/mL in genital samples over the second half of the cycle beginning with the midcycle LH surge, suggesting that genital viral load reaches a nadir before ovulation and then increases during the second half or secretory phase of the menstrual cycle. The presence of menses was not associated with increased cervical HIV RNA. Cu-Uvin presented a longitudinal study evaluating factors associated with HIV-1 RNA shedding by CVL in 97 HIV-1 infected women followed over 24 months [Abstract 784-W]. Plasma viral load was significantly associated with CVL HIV-1 RNA, with a three-fold increase in the odds of having detectable HIV in the genital tract for each log₁₀ increase in plasma viral load at baseline, an association that persisted over time. Additionally, the presence of semen in CVL at baseline was associated with detection of HIV in the genital tract (OR 13.08, 95% CI 2.55, 7.72), suggesting that some of the virus detected may be from male partners. In this study, over half of the male partners were HIV-infected.

There were also several presentations examining the male genital tract that have potential implications for sexual transmission to women. A small, prospective study examined the prevalence of HIV drug resistance in semen in men on stable HAART regimens with concomitant acute sexually transmitted disease (STDs) [Taylor, Abstract 373-M]. Previous studies in antiretroviral naïve men have shown that STDs increase seminal HIV shedding, thus facilitating HIV transmission. What has not

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been previously addressed is whether a patient with good virologic control on HAART also experiences viral rebound in the genital tract with concurrent STD acquisition and the implications this might have for the shedding of resistant virus. Six of 24 men with acute STDs had detectable virus in both the plasma and the semen at the time of infection with STDs; 4 of the 6 had detectable primary drug resistance mutations, with minimal discordance between resistance patterns in the blood and semen. Intercurrent STDs may have the ability to disrupt otherwise effective treatment, both locally in the genital tract and systemically in the plasma, and in doing so increase risk for development of drug resistance. This has implications for control of disease on an individual level, but may also have broader implications for sexual transmission of drug resistant variants.

The differential penetration of antiretroviral drugs among physiologic compartments, including the genital tract, is also important to maintain control of HIV in the individual and to prevent sexual transmission of HIV-infection. Previous studies have suggested that in general, penetration of protease inhibitors into the male genital tract is poor, while nucleoside analogs and NNRTIs penetrate well. A small study of 4 men found that lopinavir also appears to have poor penetration into semen [Sankatsing, Abstract 439-W]. Poor penetration of protease inhibitors into seminal fluid may increase the risk of sexual transmission and possible transmission of resistant strains.

Sex Differences in Viral Load and Progression

In an analysis of 9 cross-sectional and 4 longitudinal studies, viral load measurements were compared in HIV-infected men and women [Gandhi, Abstract 775-W]. After adjusting for confounders, women had consistently lower viral loads than men at similar stages of infection, which is consistent with earlier reports. Possible explanations include sex differences in immune modulation, immune function variability over the ovulatory cycle, and lower CCR5 density in women. In a retrospective cohort of 229 patients (35% women), the effect of sex on long-term durability of antiretroviral therapy and CD4 count rise was evaluated [Wilkin, Abstract

777-W]. In this analysis 7.5% of women failed to reach undetectable viral load compared with 19.5% of men ($p=.02$). Women achieved an undetectable viral load more often, even after adjusting for baseline CD4 count, viral load and prior NRTI use. Women had a lower baseline viral load ($p=.004$) and a trend toward higher CD4 counts ($p=.09$). They were also less likely to have a history of an AIDS defining illness ($p=.002$). Once reaching undetectable viral load, virologic failure did not differ by sex, and CD4 count rise after starting antiretroviral therapy was similar. There is still no compelling reason that guidelines for antiretroviral therapy should be different for women and men, however.

Metabolic Effects

The recent reports of 3 maternal deaths due to lactic acidosis in women who had been on long-term therapy including d4T and ddI led to questions about whether pregnancy might be a time of greater vulnerability to lactic acidosis. Although this question has not been answered, a study presented by Lonergan that examined the incidence of symptomatic hyperlactatemia in adults on NRTIs may add other pieces to the puzzle [Abstract 35]. The risk of this condition was found to increase more than two-fold for each additional NRTI used in a regimen; in dual NRTI-containing regimens, combinations of d4T/ABC and d4T/ddI conferred the greatest risk. With triple NRTI combinations, d4T/ABC/3TC and d4T/ddI/3TC confer greatest risk. These findings may provide some rationale for closer monitoring of symptoms and a low clinical threshold for checking lactate levels in pregnant women on NRTI regimens.

Cardiovascular disease risk is of increasing concern as a potential long-term toxicity associated with effective antiretroviral therapy. Although heart disease rates are generally lower in women than in men until after menopause, U.S. women with HIV-infection may be more likely to have risk factors for cardiovascular disease than U.S. women in general. A cross-sectional study in 74 HIV-infected women measured concentrations of cell adhesion molecules (CAM), inflammatory markers that have been associated with atherosclerotic risk [Bausserman, Abstract 693-T]. Compared with historical controls,

CAM concentrations were elevated in HIV-infected women and were related to lipoprotein concentrations, but they did not appear to be related to treatment regimen or to time on treatment. These findings may reflect an additional risk of vascular disease in HIV-infected women.

Osteopenia, osteoporosis, and osteonecrosis have also been associated with HIV-infection and its treatment. Arnsten described a cohort of 40 peri- and postmenopausal women (19 HIV-infected and 21 HIV-negative) who underwent bone density scan (DEXA) of the lumbar spine, hip, and total body [Abstract 717-T]. All HIV-infected women had taken antiretroviral therapy, and 55% had been on a regimen that included a protease inhibitor (mean duration 48 months). After adjustment for age, no association was found between HIV-infection or PI exposure and reduced bone mineral density (BMD), although the sample size was small. In a 72-week cohort study reported by Mondy, changes in BMD were evaluated in 108 HIV-infected men and 17 HIV-infected women, along with serum and urine markers of bone turnover [Abstract 718-T]. Despite a mean age of 41 years, the prevalence of bone loss was high (46%). Factors associated with decreased BMD included known risk factors for bone loss, such as steroid use, smoking, low BMI, and a history of significant weight loss or wasting. Use of protease inhibitors was not significantly associated with decreases in BMD after controlling for other risk factors.

Both of these studies suggest that well-recognized risk factors for osteopenia and osteoporosis are associated with loss of BMD density in HIV-infected individuals and that HIV-infected women are at increased risk for these conditions after menopause. Risk factors for bone loss, including menopause, should be routinely assessed in HIV-infected women, and there should be a low threshold for bone density screening.

Cervical Dysplasia/HPV

Two presentations addressed what are perhaps the most common gynecologic manifestations of HIV disease, human papillomavirus (HPV) infection and cervical dysplasia. A randomized multi-arm clinical trial compared observation versus cryotherapy in women with biopsy-



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confirmed low grade squamous intra-epithelial lesion (LSIL) and cryotherapy versus loop electrosurgical excision procedure (LEEP) in women with high grade squamous intra-epithelial lesion (HSIL) [Wright, Abstract LB16]. Women who had unsatisfactory colposcopy had either cervical conization or LEEP. One hundred and twenty-two HIV-infected and 257 HIV negative women were included. Mean follow-up was 10 months for HIV-infected women and 11 months for women without HIV. All treatment modalities were less effective in women with HIV-infection than in women without HIV, and no single treatment type appeared to be superior. Although HIV-infected women with LSIL had significantly lower spontaneous

regression rates (24%) than HIV negative women (61%), the rates of progression to biopsy-confirmed HSIL were low in both groups (4% vs 9%, respectively, p=NS). Only 56% of HIV-infected women with LSIL who were treated with cryotherapy had normal findings at follow-up, compared to 95% of HIV negative women with LSIL and cryotherapy. These findings are not surprising in light of previously published studies, but do suggest that conservative observation of confirmed LSIL is the most reasonable course of action.

Ellerbrock and colleagues examined serial vaginal HPV-DNA levels in 40 HIV-infected women with at least 3 months of follow-up [Abstract 119]. There were no significant differences between women on

successful HAART (consistently undetectable plasma viral load) compared with those not on HAART in the proportion with increased, decreased, or unchanged HPV DNA levels. In multivariate analysis, HAART had no effect on HPV DNA level after controlling for CD4 count and plasma viral load. Although limited by small numbers and short follow-up, this study contributes to a growing body of literature suggesting that effective antiretroviral therapy is not going to have a dramatic impact on HPV infection or progression of cervical dysplasia, and close monitoring will be required.

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HIV in Pregnancy

• HIV Rapid Tests

The goal of providing optimal care for HIV-infected pregnant patients in labor is often hampered by the lack of an HIV diagnosis at presentation. Women may not have been tested during prenatal care, may have been infected later in pregnancy, or may not have received prenatal care. Two presentations addressed the practicality of using rapid tests to identify previously undiagnosed HIV positive pregnant patients followed by initiation of appropriate intrapartum antiretroviral therapy. Over 3500 women were tested in a study in Peru [Santos, Abstract 789-W] and over 1700 women were tested in a study in Brazil [Melvin, Abstract 788-W]. In the Brazilian study results suggested that rapid tests had a high sensitivity (100%) and specificity (99.3%), with a negative predictive value of 100%. Occasional false positives emphasize the importance of confirming positive results with standard testing; however, this should not delay prophylactic treatment to reduce mother-to-child transmission. While use of rapid testing in the labor and delivery suite can play a role in reducing the risk of vertical transmission, the importance of providing adequate pre- and post-test counseling and adequate follow-up for these patients should not be overlooked.

• Vertical Transmission

The increased use of HAART during pregnancy coupled with elective Cesarean section has led to significant declines in vertical transmission rates in the U.S. and Europe. The PACTG 367 study found an overall perinatal transmission rate of 3.6% in 2087 pregnancies between 1998 and 2000 [Shapiro, Abstract 114]. Transmission rates were then analyzed by use of antiretroviral therapy, regimen type, mode of delivery, and viral load. Combination antiretroviral therapy was associated with the lowest transmission rates at all viral load strata. Among women with viral load <1000 c/mL near the time of delivery, transmission rates were less than 1%, regardless of mode of delivery or type of antiretroviral therapy used. These findings provide information that is useful when counseling pregnant women or HIV-infected women who are considering pregnancy.

Eighteen month follow-up data from the HIV-NET 012 study demonstrated

continued efficacy of single dose nevirapine for mother and infant, with 41% efficacy compared to intrapartum/postpartum AZT [Fowler, Abstract 120]. A subgroup analysis of the HIVNET 012 data demonstrated efficacy, even among women with the highest viral loads and the lowest CD4 counts. Among women with viral loads greater than 50,000 c/mL, the relative risk of transmission for those on AZT was 1.9 (1.2-3.3) compared with those on NVP. Late efficacy of the NVP regimen is comparable to that seen with other abbreviated regimens.

• Resistance

Drug resistant HIV in pregnancy and its relationship to perinatal transmission and future maternal health remains a problem. In a retrospective blinded study examining the prevalence of drug resistance among HIV-infected infants born in New York State between 1998 and 1999, 11 of 91 (12.1%) had mutations associated with antiretroviral therapy resistance [Marker, Abstract 800-W]. Among these infants, 2.2% had mutations associated with resistance to two classes of drugs; 7.7% had mutations associated with NRTI resistance, 3.3% to NNRTI resistance, and 3.3% to PI resistance. Interestingly, perinatal antiretroviral exposure was not a significant determinant of genotypic resistance in this cohort of infected infants. However, for infants with drug resistant mutations and perinatal antiretroviral exposure, specific mutations were correlated with at least one agent used in the perinatal period. In a follow-up from the PETRA study, in which HIV-infected women received one of three short-course regimens containing AZT/3TC, 2/24 (8.3%) women who received antepartum, intrapartum and postpartum ZDV/3TC had the M184V mutation one week after delivery with reversion to wild type virus by 3 months [Giuliano, Abstract 802-W]. The presence of this mutation was not associated with vertical transmission. Resistance mutations were not identified in women who received intrapartum and postpartum prophylaxis only. It is clear that we must be particularly vigilant in monitoring long-term maternal outcomes and outcomes of subsequent pregnancies after use of monotherapy or dual nucleoside therapy, even in abbreviated regimens. Taken together, these studies emphasize the importance of appropriate HIV counseling and testing in women during the

preconception and antenatal period to ensure both optimal maternal treatment and perinatal prophylaxis.

Conclusions

In the end, the studies discussed above offer the following “take-home” messages:

1. It is increasingly clear that a better understanding of the relationship between genital tract HIV and other parameters, including plasma viral load, antiretroviral therapy use, hormonal milieu, and genital tract infections (including those not generally sexually transmitted) is crucial to the reduction of sexual transmission risk, as well as to achieving optimal control of HIV in infected women.
2. As data accumulate regarding long-term metabolic effects of HIV and antiretroviral treatment, clinicians must consider the special risks women may face, particularly during pregnancy or after menopause.
3. Antiretroviral therapy, while very effective in treating HIV, does not appear to be very effective against HPV infection. On the other hand, the presence of LSIL, the most common cytologic abnormality, does not require specific treatment, although the need for careful follow-up remains.
4. In pregnant women, plasma viral load appears to be the key determinant in risk of mother-to-child transmission, regardless of mode of delivery or type of antiretroviral therapy used. HIV RNA level <1000 c/mL was associated with a <1% transmission rate. This is consistent with what many obstetricians have long believed and advocated. Cesarean delivery need not be routine for HIV-infected women, and greater emphasis should be placed on appropriate antiretroviral therapy for both maternal and fetal health.
5. The efficacy of single-dose nevirapine to mother and newborn in preventing mother-to-child transmission persists at least through 18 months even in those women at highest risk for transmission because of high viral load and low CD4 counts.
6. Drug resistance in pregnant women and in infected infants continues to be an issue of concern related to transmission risk and longer term treatment outcomes in women. Although resistance can be seen in the absence of antiretroviral exposure, there are specific concerns in women exposed to abbreviated dual nucleoside or monotherapy during pregnancy. ▲



HLA B57 and Abacavir Hypersensitivity

By Charles Flexner, M.D.

The sequencing of the human genome has focused much attention on finding genetic causes for both common and uncommon diseases. The field of pharmacogenetics (or pharmacogenomics) identifies genes associated with drug responsiveness. So far, this field has produced little of real clinical consequence.

One of the most dramatic pieces of pharmacogenetic research involving any drug was unveiled at the 9th CROI. Teams of investigators from GlaxoSmithKline and Western Australia, working independently, identified a strong association between a rare HLA type and the risk of developing abacavir hypersensitivity.

Abacavir hypersensitivity reaction (AHSR) is characterized by fever, rash, abdominal complaints, and lethargy, symptoms that almost always occur within the first six weeks of starting the drug. Fortunately, this syndrome is rare, affecting only 4-5% of recipients. However, AHSR may be fatal, especially if the drug is discontinued and then restarted. The low incidence of AHSR, its time-course, and its greater severity with re-challenge prompted speculation that it might be genetically linked. It has also been shown that AHSR occurs less frequently in African-Americans than in Caucasians. This focused attention on genes controlling immune response, which have previously been associated with severe hypersensitivity to sulfa drugs.

A team of immunologists and geneticists in Western Australia had a unique opportunity to study this connection when abacavir was first introduced into their province a few years ago. There is only one large city (Perth), and most HIV-infected patients are treated at a handful of clinics. Further, most inhabitants of this province are of English or Irish decent, and this ethnic homogeneity makes it easier to pick out genes that might be associated with rare conditions.

This team identified 18 cases of AHSR in 200 treated patients. They developed a very stringent case definition for AHSR, excluding 15 patients with borderline or partial symptoms, and leaving 167 controls [Mallal, Abstract 91]. They then examined the HLA and DR regions (associated with regulating immune response) in all 200 patients, and discovered that 14 cases (78%) but only 4 controls (2%) had a rare HLA type, B5701. This HLA type is present in

Table. Association Between HLA Type and Risk of Abacavir Hypersensitivity (Adapted From Mallal et al., *Lancet* 2002;359:727).

Genotype	Abacavir Hypersensitive	Abacavir Tolerant	Odds Ratio (95% C.I.)
HLA B5701	14/18 (78%)	4/167 (2%)	117 (29-481)
HLA DR7 + HLA DQ3	13/18 (72%)	6/167 (3%)	73 (20-268)
HLA B5701 + HLA DR7 + HLA DQ3	13/18 (72%)	0/167 (0%)	822 (43-15,675)

8% of Irish Caucasians, but in only 2.4% of African Americans. The odds ratio for this association, 117, was highly statistically significant. The combination of HLA B5701 plus two other loci, HLA-DR7 and HLA-DQ3, was present in 13 of the cases but none of the controls, for an odds ratio of 822! (See table, above.) This genetic association is as strong as that between HLA B27 and ankylosing spondylitis.

An article describing the full results of this study was published in the *Lancet* on the same day the presentation was made [2002;359:727]. One interesting conclusion of this article is that HLA B5701 is probably not the causative gene, but is linked to another genetic region encoding a family of human heat shock proteins (HSP), which is the more likely culprit.

A second group of investigators from GlaxoSmithKline performed a retrospective analysis of DNA samples collected from patients suffering from AHSR in company-sponsored trials and compared them to matched controls [Hetherington, Abstract 92]. After establishing a rigid case definition similar to that used by the Australians, they identified 50 cases of AHSR and matched them (by race, sex, and CD4 count) to 80 controls. They examined 114 candidate genes associated with drug metabolism and immune responsiveness, and found the same association as the Australian group: HLA B57 was most strongly associated with AHSR, occurring in 46% of cases but only 4% of controls. There was also a strong association between a point mutation (SNP) in the tumor necrosis factor- α (TNF- α) gene and AHSR. However, as was pointed out in both this presentation and in the *Lancet* article, the TNF- α SNP and HLA B57 genes are linked, which suggests that this is probably a secondary, rather than a primary association.

It is important to point out several caveats about both of these studies. First, genetic linkages are highly dependent on the population studied, hence the stronger B57 association in the Western Australian patients. In fact, the majority of the AHSR cases in the GSK study were not HLA B57 positive. This emphasizes the complex nature of these genetic associations, and the fact that more than one gene may be involved.

HLA B5701 should not be used as a diagnostic test for abacavir hypersensitivity, since the majority of U.S. patients (especially non-Caucasians) who have the syndrome will not have the gene. However, in a largely English-Irish community, such as that in Western Australia, having HLA B5701 places a patient at high risk for developing AHSR. Many patients in that province are now being screened for HLA B5701 prior to starting abacavir, and the drug is avoided in those who have the gene. In Western Australia, this will reduce the overall risk of AHSR by nearly five-fold, while denying abacavir treatment to only a handful of patients.

The use of genetic screening to avoid AHSR in ethnically diverse places like Baltimore will require much more work. Still, these two studies have brought HIV care providers into the genetic age, ready or not. ▲

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Selected talks from the
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IQ's, VIQ's, and NIQ's: Are We Smart Yet?

By Charles Flexner, M.D.

Therapeutic drug monitoring (TDM) for antiretrovirals remains one of the most interesting and controversial topics in HIV pharmacology. Several presentations at the 9th CROI reflected recent progress in thinking about how to make TDM clinically useful.

Inhibitory Quotients versus Drug Levels

Most TDM studies have examined the association between a patient's drug concentrations and the likelihood of deriving viral load benefit from that drug. Virologists have long argued that this only works for treatment-naïve patients with drug-sensitive virus. Different rules about drug levels must apply to patients with

Table: Three Ways to Measure an HIV Inhibitory Quotient for Anti-HIV Drugs.

Abbreviation	How Calculated
IQ = Inhibitory Quotient	$\frac{C_{\min}}{IC_{50}}$ (trough concentration) IC ₅₀ (based on phenotype)
VIQ = Virtual Inhibitory Quotient	$\frac{C_{\min}}{\text{Virtual } IC_{50}}$ (based on genotype)
NIQ = Normalized Inhibitory Quotient	$\frac{\text{Patient's VIQ}}{\text{Population mean VIQ}}$ (Using average C _{min} and average IC ₅₀ for drug-sensitive HIV)

complex treatment histories and drug-resistant HIV.

Three studies presented in an oral abstract session predicted treatment outcome by using a ratio of patients' drug concentrations and their phenotypic sensitivity. The inhibitory quotient, or IQ, is a previously described ratio of the patient's drug trough concentration (C_{min}) and the drug concentration required to inhibit that patient's virus by 50% *in vitro* (IC₅₀; see table, above). Two other IQ's were presented: A virtual IQ (VIQ) and a normalized IQ (NIQ).

In an analysis of ACTG Protocol 359, Courtney Fletcher and colleagues from the University of Minnesota examined saquinavir (SQV) trough concentrations and measured SQV IC₅₀'s in 32 heavily treatment-experienced patients taking SQV plus ritonavir (RTV) or nelfinavir (NFV) as part of salvage therapy [Abstract 129]. Although SQV levels alone correlated poorly with virologic response, the SQV IQ (the ratio of trough to phenotypic IC₅₀) more strongly predicted early treatment response. The mean IQ was 201 in those with viral loads below baseline at week 4, but only 17 in those with viral loads at or above baseline.

IQ correlated with viral load response out to week 12, but by week 16 the correlation was no longer significant. This may be because patients were heavily pre-treated and destined to fail anyway, especially given the unconventional regimen, which included delavirdine (DLV) and adefovir. It should also be noted that the investigators were looking at only one drug in a 4-drug regimen.

In a second study with 24 heavily pretreated patients, investigators from Vancouver and Toronto measured the association between virologic outcome and the "virtual" IQ (VIQ) in patients treated with a salvage regimen containing lopinavir/ritonavir (LPV/RTV) plus amprenavir (APV) [Phillips, Abstract 130]. They measured LPV and APV troughs, and then measured IC₅₀ using the "virtual" phenotype, which estimates IC₅₀ from genotype. After at least three months of treatment, the median VIQ for APV was 5.2 in patients with a viral load of <50 c/mL, versus 0.9 in those with detectable viral loads. Similarly for LPV, median VIQ was 12.3 for those with undetectable viral loads versus 1.8 for those with detectable viral loads. Twelve of twelve patients who had a greater than one log drop in viral load on LPV had a VIQ >5.0, suggesting that this might be a reasonable target for TDM.

A third study conducted in Italy looked at the LPV IQ in 52 patients failing a previous PI-containing regimen, using a parameter called the normalized IQ (NIQ) [Castagna, Abstract 128]. In this study, the NIQ was calculated by comparing the patient's VIQ (using the Virco *VirtualPhenotype* assay) to a "population" VIQ, which is the mean LPV trough (C_{min}) from previous large studies in patients given the same dose of LPV/RTV, divided by the mean IC₅₀ in a population of viruses deemed sensitive to LPV (based on the *VirtualPhenotype* assay). The advantage of this assay is that it compares the patient's IQ to drug-sensitive patients with "normal" trough concentrations. The disadvantage is that the NIQ involves somewhat arbitrary decisions about what

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IQ's, VIQ's, and NIQ's: Are We Smart Yet?

is a “normal” comparative patient population, and what constitutes sensitive or resistant virus. In this study, NIQ was more predictive of viral load outcome at 48 weeks than resistance testing alone, and was in fact more predictive of viral load outcome than any other parameter except baseline viral load ($p < 0.001$, mixed effects model). When patients were divided up into quartiles, those with an NIQ of < 0.6 had a median viral load drop of 0.7 logs at week 48, compared to a 2.8 log drop in those with an NIQ of > 14.5 . Interestingly, in this study, LPV trough concentrations were not associated with treatment outcome at all.

Taken together, these studies suggest that TDM strategies in treatment-experienced patients will need to factor in resistance as well as drug concentrations. This is probably not surprising, but these studies provide some initial guidelines for what IQs (or VIQs or NIQs) should look like.

All three of these studies were small, and one of the studies used a different method to correct for protein binding of the involved drug. However, as was pointed out, if the protein binding correction is consistent within an assay, it becomes a constant and is therefore only relevant if comparing one company's assay with another's. Finally, none of these studies was a prospective TDM trial; they all examined the correlation of baseline IQ to outcome without adjusting anyone's drug dose (or changing regimen) to try and achieve a higher IQ. Two of the three studies found that drug concentrations alone—the basis for traditional TDM—did not predict treatment outcome, suggesting that TDM might be a waste of time in treatment experienced patients.

Along those lines, there was more bad news for TDM at the 9th CROI with release of the results of the GENOPHAR Study [Bossi, Abstract 585-T]. This prospective French trial randomized 134 patients failing therapy to a genotypically guided salvage regimen with or without the addition of TDM information to guide dosing. At the end of 24 weeks, 52% of genotype-only patients and 60% of genotype+TDM patients had a viral load of < 400 c/mL, a difference that was not statistically significant.

Unfortunately, GENOPHAR had many of the same design flaws as

PharmADAPT, another prospective TDM trial with negative results that was presented at the 8th CROI. Neither study modified regimens based on pharmacokinetic results until week 8, and both were conducted in a heavily pretreated population with poor prognosis and possibly poor adherence from the outset.

The addition of IQ testing to TDM strategies may make us smarter in the future about how we manage our patients, especially in salvage. But whether we are smart enough to make TDM work to improve outcomes in the clinic will require more examination.

More Pharmacology: QD versus BID *Kaletra*

LPV/RTV (*Kaletra*) has become a popular PI for both initial and salvage therapy, owing in large part to its potent inhibition of most HIV isolates and its high IQ (see above). LPV/RTV is currently dosed twice-daily, although the long apparent half-life of LPV in the presence of RTV suggests its possible use as a once-a-day drug. The first pharmacokinetic and efficacy data on qd LPV/RTV compared to the twice-a-day drug were presented at the 9th CROI and looked promising.

Rick Bertz and colleagues from Abbott Laboratories presented data showing that six capsules of *Kaletra* (800/200 mg LPV/RTV) given once-daily produced a 24-hour area under the concentration-time curve (AUC_{24}) similar to that produced by three capsules (400/100 mg) given every 12 hours [Abstract 126]. However, the qd regimen produced a trough (C_{min}) at the end of 24 hours that was about half that seen with the bid regimen.

IQs were still high (40 on average with the qd regimen and 84 with the bid regimen), but there was more variability in troughs with the qd than with the bid regimen. Two patients in the qd arm had IQs of < 10 , while the lowest IQ with the bid regimen was 36.

Despite these differences, treatment outcome after 48 weeks in 38 treatment-naïve patients was similar: 79% of bid patients had a viral load < 50 c/mL versus 74% treated with qd [Abstract 409-W]. Larger and longer comparisons of qd versus bid LPV/RTV are still needed, especially in treatment-experienced

patients, for whom these results might be irrelevant.

Drug Interactions

• **Amprenavir, Ritonavir, and Efavirenz:**

These three drugs are sometimes given together in salvage regimens. Investigators from GlaxoSmithKline, Johns Hopkins, Buffalo, and Albany examined the interaction between the APV prodrug GW433908 at a dose of 700 mg bid with efavirenz (600 mg qd) and RTV. The addition of efavirenz did not reduce APV concentrations if subjects were taking either 100 or 200 mg RTV bid. However, this regimen was associated with increases in both cholesterol and fasting triglycerides at weeks 2 and 4 in these 32 healthy seronegative volunteers [Wire, Abstract 431-W].

• **Amprenavir and Delavirdine:** Recent cross-sectional studies have found that APV can reduce LPV concentrations by 25% or more, suggesting that APV might serve as a cytochrome P450 3A4 inducer for some drugs. A study from Denmark [Justesen, Abstract 442-W] showed that APV 600 mg bid reduced the DLV (600 mg bid) steady-state AUC by 60%, and reduced the DLV trough by almost nine-fold. This suggests that APV can significantly induce DLV metabolism, and the investigators recommend that APV and DLV not be given together at these doses.

• **Ritonavir and 2D6:** Ritonavir is a potent inhibitor of drug metabolism mediated by the cytochrome P450 3A4 enzyme. It is also a moderate inhibitor of the cytochrome P450 2D6 isoform *in vitro*. 2D6 is an enzyme involved in the metabolism of a number of anti-depressant and psychoactive substances, and the clinical significance of RTV's potential to inhibit 2D6 has been of some concern. Investigators from Abbott Laboratories found that LPV/RTV, which contains 100 mg RTV per dose, did not significantly alter the pharmacokinetics of desipramine (100 mg) in healthy volunteers [Preston, Abstract 433-W]. Desipramine is an antidepressant and a pure 2D6 substrate and is a good indicator of the potential of RTV to act as a clinically significant 2D6 inhibitor. This study suggests that a 100 mg bid dose of RTV (or RTV/LPV) can be co-administered safely with most 2D6 substrates. ▲



TB and HIV: Challenges and Progress

By Richard E. Chaisson, M.D.

Tuberculosis took center stage at the 9th CROI, but there was little good news to report. In a special symposium, four speakers addressed important new scientific developments in the area of TB and its control. Dr. Nulda Beyers of the University of Stellenbosch, S. Africa, reported on the innovative epidemiologic research her group has been carrying out, largely in HIV-negative patients [Abstract S5]. Using DNA fingerprints, she and her colleagues have determined transmission dynamics of TB in a developing country setting, noting a few surprises. While conventional dogma has it that TB is transmitted in the home, Beyers has found that much transmission occurs outside the home. Over 60% of TB in her study is recently transmitted, but within households experiencing more than one case of TB, two-thirds of patients have unrelated strains of TB, implying that infection was acquired outside the home. Community studies reveal that much TB is spread in the setting of alcohol use, often in bars and other social settings. Beyers also reported that a large proportion of recurrent TB in her community was from re-infection, not relapse (even among HIV-negative patients). She also pointed out that rates of transmission in the community are so high (>3.5% per year), that virtually all adults are infected. This means that the introduction of a highly effective new TB vaccine will have no impact on TB incidence for an entire generation. As HIV enters this community, the situation will get even worse.

Dr. Chris Whalen of Case Western University discussed interactions of TB and HIV, based largely on the studies carried out with his colleagues at the Makkerre University in Kampala, Uganda [Abstract S6]. He noted that a bi-directional interaction exists with TB and HIV, each pathogen increasing the pathogenicity of the other. HIV decreases immune control of latent TB infection, greatly increasing the risk of reactivation to active disease. Conversely, TB upregulates HIV expression through several mechanisms, including release of pro-inflammatory cytokines such as TNF and IL-6. As a result, the natural history of each infection is exacerbated by the other. Whalen showed that patients with HIV who develop TB have higher rates of subsequent disease progression, measured both by decline in CD4 count and rates of opportunistic infections and death. In

discussing management options, Whalen presented the results of a recent controlled trial of prednisone in patients with HIV-related TB receiving anti-TB but not antiretroviral therapy. The hypothesis of the study was that treatment with prednisone would reduce the production of pro-inflammatory cytokines and lessen the impact of TB on HIV disease. Paradoxically, patients receiving prednisone had significantly greater increases in both CD4 count and viral load, but the differences disappeared after the drug was discontinued. Whalen concluded that the most effective means for managing TB during HIV was to treat with antiretrovirals.

Joanne Flynn of the University of Pittsburgh next presented an overview of TB vaccine development [Abstract S7]. She described the complex host responses to TB infection, and the importance of both CD4 and CD8 cells in controlling infection. She noted that a successful vaccine would need to provide as good or better protection against disease as natural infection. Ironically, natural infection is contained by more than 90% of infected people (except in HIV-infection), and efforts to improve on this have proved difficult. The current TB vaccine, BCG, is not thought to provide protection against pulmonary TB in adults in most settings. In animal models, however, BCG reduces TB in tissues by 1-2 logs. Most new vaccine candidates in recent years have been less effective than BCG, however. There are a number of new TB vaccines in the pipeline, including a few that have been more effective than BCG in animals. Flynn was cautiously optimistic about prospects for producing an efficacious new vaccine, and predicted that clinical trials of several candidates would begin in the coming several years.

Dr. Gary Maartens of the University of Cape Town, South Africa gave the closing talk of the symposium, in which he addressed the impact of the TB and HIV epidemics in sub-Saharan Africa [Abstract S8]. He noted that Africa has 8% of the world's population but 18% of its TB cases and 71% of its HIV-infections. The collision of these epidemics has been catastrophic, with escalating case rates leading to an overburdening of clinical services and high mortality. Maartens discussed some of the clinical dilemmas in HIV-related TB, especially the problem of

smear-negative disease. Patients with negative sputum smears may have TB or another infection that requires different therapy. Mortality in these patients is very high when they are treated for TB, either as a result of advanced AIDS with a failure to respond to treatment, or because they actually have another disease that is fatal when left untreated. Maartens reviewed clinical algorithms for managing these patients, including empiric therapy for bacterial pneumonia before a trial of anti-TB treatment. He also discussed management of HIV disease in TB patients in a high burden setting, emphasizing the importance of trimethoprim-sulfa treatment to reduce mortality. Data from South Africa confirm findings of a clinical trial in the Ivory Coast which showed that TMP-SMX reduces mortality in HIV/TB patients significantly. Another important approach to controlling the dual epidemics is to increase diagnosis of TB in HIV-infected populations. Among HIV seropositive patients in Voluntary Counseling and Testing (VCT) centers in Cape Town, 8% were found to have active TB and another 29% were either on TB therapy or had recently been treated for TB. Maartens was not enthusiastic about preventive therapy for TB in African patients with HIV, citing an analysis that showed that 19 tuberculin-positive patients with HIV would need to be treated to prevent one case of active TB. He concluded with data demonstrating the impact of antiretroviral therapy on TB incidence. Patients receiving HAART in Cape Town had an 84% reduction in TB incidence compared to patients treated with one nucleoside analogue or no antiretrovirals, similar to the data from the U.S. and Europe. He concluded that massive efforts were required to bring the necessary clinical services to the millions of people with HIV and TB in Africa.

Several other TB presentations were included in the poster sessions. Girardi and colleagues from GISTA-SISMIP study group in Italy reported that 5% of 129 initially tuberculin negative patients who had responded to HAART converted their skin tests after a mean of 31 months on treatment [Abstract 624W]. Conversions were not associated with anergy at baseline, but were strongly related to CD4 count at the time the second test was applied:



TB and HIV: Challenges and Progress

6/7 converters had a current CD4 count of $>200/\text{mm}^3$. They recommended retesting tuberculin negative patients who have responded to HAART when the CD4 count rises to above $200/\text{mm}^3$. Girardi and associates also presented data on HIV-infected patients who developed TB in the era of HAART [Abstract 623W]. Of 272 TB/HIV-infected patients identified between May 1999 and September 2000, one-third were immigrants to Italy, half were injection drug users, and 16% had a previous TB diagnosis. HIV was diagnosed at the time of TB diagnosis in 30%, and 40% were not receiving antiretrovirals at the time of TB diagnosis. Failure to treat known latent TB was responsible for only 5% of cases.

Rivero and colleagues presented data from a controlled trial of TB prophylaxis in HIV-infected, anergic patients [Abstract 625W]. Three hundred-nineteen patients

were randomized to receive INH for 6 months, INH-rifampin for 3 months, rifampin-PZA for 2 months or no treatment. Rates of TB per 100 person-years were, respectively, 3.4, 3.1, 1.2 and 3.1. The authors concluded that preventive therapy was not effective and was not necessary in this population. The rates of reported TB, however, are for the most part fairly high, so the conclusion that preventive therapy is not needed is unwarranted, in my view. A number of studies have shown a lack of benefit from preventive treatments in anergic patients, but several, like this trial, show that the risk remains high. One possible explanation is that the patients are acquiring new TB infections after they finish their prophylaxis, in which case infection control measures may be more important than preventive treatment.

A final study of TB and HIV was reported by Hung and colleagues from

Taiwan [Abstract 636W]. They compared the clinical course of 116 HIV-infected patients who developed TB with 525 HIV patients without TB. Patients with TB had lower initial CD4 counts (median 32 vs. 71), higher viral loads (310,000 vs. 76,000), and were more likely to be immigrants to Taiwan and to have acquired HIV heterosexually. Prior to the introduction of HAART, TB patients had slightly greater mortality rates than non-TB patients, but these differences disappeared after the advent of HAART. Among patients treated with HAART, TB patients had similarly good responses compared to non-TB patients, with the majority achieving an undetectable viral load. The authors concluded that TB has no adverse effect on HIV course and that response to HAART is not impaired by TB or TB drugs. They recommended that HAART be initiated early in patients with HIV-related TB. ▲

Update on Opportunistic Infections

By John G. Bartlett, M.D.

At present, discontinuation of primary prophylaxis for PCP, toxoplasmosis, and MAC after an adequate response to HAART is recommended as safe (AI recommendation) according to the 2001 USPHS/IDSA guidelines (available at <http://www.hivatis.org>). Secondary prophylaxis refers to the use of prophylactic agents to prevent a recurrence of disease once a patient has been adequately treated for the primary episode. Discontinuation of secondary prophylaxis after an adequate response to HAART is supported by fewer data, and is a BII recommendation for PCP and a CIII recommendation for toxoplasmosis and MAC. Data presented at the 9th CROI lend support to discontinuing secondary prophylaxis after an adequate response to HAART, although recurrences of disease do occasionally occur.

Mussini and colleagues reported three relapses among 58 patients with cryptococcal meningitis when secondary prophylaxis was discontinued [Abstract 635-W]. However, scrutiny of the three cases showed that the etiologic diagnosis was based only on recurrence of cryptococcal antigen in serum, and others have concluded this antigen assay is not a good test for long term follow-up of cryptococcosis. Bertschy and co-workers reported a relapse of toxoplasmosis in one of 14 patients after secondary prophylaxis was discontinued [Abstract 633-W]. Discontinuation of secondary prophylaxis for cryptococcosis and MAC after immune reconstitution also appears to be safe, although there are rare breakthroughs. Aberg reported results from ACTG 393, in which 48 patients discontinued secondary prophylaxis for MAC [Abstract 634-W]. There was one case (2%) of MAC osteomyelitis of the rib at 16 months in a patient with a CD4 count of $244/\text{mm}^3$, which represents a recurrence but should probably be considered a manifestation of "the immune reconstitution syndrome." Burman reported 24-month follow-up data on 520 patients with a median CD4 count of $261/\text{mm}^3$ after a median nadir of $24/\text{mm}^3$ [Abstract 631-W]. There were 17 deaths, but 12 were unrelated to HIV. One patient developed MAC bacteremia, but only after the CD4 count decreased to $21/\text{mm}^3$.

Data continue to confirm that HAART-induced immune reconstitution leads to protection from OIs, with only occasional exceptions. Koletar and colleagues provided data on 643 patients who were followed for a median of 153 weeks after discontinuing MAC prophylaxis when the CD4 count increased from <50 to $>250/\text{mm}^3$ [Abstract 630-W]. The subsequent increase in CD4 count correlated with viral suppression: There was a median increase of $9/\text{mm}^3$ every 8 weeks in patients with undetectable viral loads vs no change in patients with consistently detectable viral loads. There were 27 AIDS-defining events, including 10 in patients with CD4 counts $>200/\text{mm}^3$, 3 with presumed PCP, 2 with CMV, and 2 with cryptosporidiosis.

With rare exceptions, the results of these studies add to an already robust database that demonstrates that viral suppression and CD4 rebound substantially reduce the risk of HIV-associated complications. ▲



Adolescence is a stage of life typically characterized by good health, with healthcare encounters focused on health maintenance and issues surrounding prevention of STDs, drug use, and unwanted pregnancy. Adolescent health care providers in geographic regions hard hit by HIV are now faced with two important trends. First, a large cohort of youth infected by birth and sustained by HAART is coming of age and in need of specialized medical care, including counseling and services to address their reproductive health choices. Secondly, uninfected youth are entering a phase of their lives in which their behavior choices, coupled with social vulnerabilities that might not be apparent to the health care provider, could dramatically increase their risk of HIV-infection. To date, high rates of HIV have been described in young men who have sex with men, young injection drug users, and homeless or runaway youth who engage in these transmission behaviors. Heterosexually acquired HIV among female youth is a growing problem, but identifying specific characteristics of those at risk remains a challenge. The aim of the newly organized NIH-funded Adolescent Trial Network (ATN) is to develop effective methods of enhanced case finding for HIV-infected youth and to develop and test prevention interventions for the most vulnerable youth. This article will discuss rates of HIV testing among youth, surveillance data on HIV-infection among adolescents in the U.S. as well as the limitations of those data, and Protocol 016 of the ATN, which is designed to systematically identify infected and at-risk youth in highly impacted U.S. cities.

Targeting Prevention to Vulnerable Adolescents

Effective primary HIV prevention trials should target individuals at significant risk for becoming infected with HIV. A means to identify these individuals is to examine the characteristics of recently infected individuals. However this approach is limited by ascertainment bias. Testing programs systematically miss infected subpopulations of individuals. In addition, testing programs fail to collect or make available data about infected individuals beyond age, race, gender, residential zip code area, and route of transmission. For

Table. Reported AIDS Cases in Adolescents and Young Adults Through 2000 by Exposure Category

Exposure Category	Male, 13-19yr N (%)	Female, 13-19yr N (%)	Male, 20-24yr N (%)	Female, 20-24yr N (%)
MSM	803 (34%)	NA	11,993 (62%)	NA
MSM/IDU	123 (5%)	NA	2,023 (10%)	NA
IDU	148(6%)	227 (13%)	2,353 (12%)	2,015 (26%)
Heterosexual contact	107 (5%)	877 (52%)	973 (5%)	4,233 (55%)
Hemophilia	756 (32%)	13 (1%)	663 (3%)	16 (<1%)
Transfusion recipient	95 (4%)	98 (6%)	107 (1%)	116 (2%)
Other/Undetermined	334 (14%)	480 (28%)	1,387 (7%)	1,353 (17%)

Abbreviations: MSM, men having sex with men; IDU, injection drug user.

example, while age, race, and residential zip code area provide information on those least likely to be infected with HIV, these variables do not provide accurate information on which individuals are in fact infected.

Concerns about these limitations may be purely academic in regions and populations where the prevalence of HIV is relatively high, as in the case of African-American men who have sex with men in large urban U.S. cities or among women of childbearing age in certain Sub-Saharan African countries. However these limitations may be profound when targeting prevention efforts at heterosexual adolescent females in the U.S. The relatively low prevalence of infection among adolescent girls, even those of color residing in impoverished communities, means that in order for prevention programs to be cost effective, policy makers and programs need to stratify the populations further than what current testing coverage and epidemiologic data can support.

Epidemiology of Adolescent HIV and AIDS in U.S.

Cumulative AIDS cases for younger age groups reported to the CDC through 2000 by probable transmission category are shown in the table above. Comparative case rates of HIV-infection for 34 U.S. regions

with HIV reporting requirements are shown for males and females by age strata in the figure below (p. 11). In 2000 alone, there were 1688 cases of AIDS reported among 13-24 year-olds, 729 of whom were female. The majority (75%) of the female cases was among 20-24 year-olds and was attributed to heterosexual contact. Forty percent of female cases among 13-19 year-olds in 2000 was due to heterosexual contact, and in 51% the risk was "not reported or identified," an exposure category often equated with heterosexual contact. The percentages of female cases among 20-24 year-olds assigned to these two exposure categories are not much different than those seen among 13-19 year olds: 47% and 40%, respectively. In contrast, only 9% and 25% of male cases among 13-24 years olds are attributed to heterosexual contact or unidentified/unreported risk.

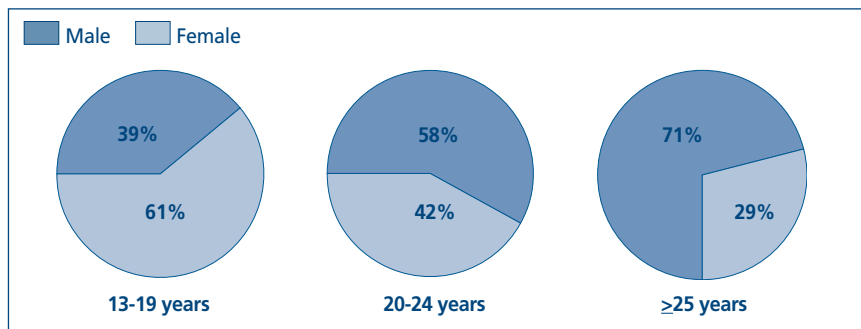
The most recent data available on racial/ethnic distribution of female adolescent AIDS cases are from 1998. These data reveal that most female adolescent cases occurred among racial/ethnic minorities. In 1998, 447/688 (65%) female AIDS cases among 13-24 year olds were black, not Hispanic, 110/688 (16%) were Hispanic, and 123/688 (18%) were white, not Hispanic.

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Reported HIV* in Adolescents and Adults, by Sex and Age at Diagnosis, 2000, U.S.



*From the 34 areas with confidential HIV case surveillance for adults and adolescents in 2000.

A review of incident HIV-infection data in the U.S. reveals demographic and exposure patterns similar to those seen with AIDS data. In 2000, 38% and 57% of female cases among 13-19 year-olds were attributed to heterosexual contact and unidentified risk, respectively. The percentage of female cases among 20-24 year-olds assigned to those two exposure categories were 38% and 53%, respectively. While surveillance data are not available for incident HIV cases by age, gender, and race/ethnicity annually, cumulative HIV cases through December 2000 show that the majority of HIV cases among 13-19 year-olds and among 20-24 year-olds occurred among black, non-Hispanic youth: 2320/3167 (73%) and 4284/6407 (67%), respectively.

Vulnerability of Female Youth to HIV

Sexually active female teenagers may be biologically more susceptible to HIV acquisition than older women for several reasons. They tend to have the highest age-specific rates of both gonorrhea and chlamydia, infections that cause cervical inflammation, and may increase the relative risk of acquiring HIV 2-3 fold. Independent of other STDs, the less mature cervix of an adolescent commonly has larger areas of cervical ectopy than that of a more mature woman. Increased cervical ectopy has been associated with increased HIV acquisition in several reports [Moss GC et al. *JID* 1991;170:313]. Age-discrepant sexual relationships (i.e., female teens having much older sex partners) have been associated with higher rates of teen pregnancy, STDs, as well as HIV acquisition among teen girls [*MMWR* 2000;49:861].

Rates of HIV Testing Among Youth

There is growing evidence that many youth are not accessing or receiving HIV testing, which may be contributing to an ascertainment bias in surveillance data. In a study of Massachusetts households, adolescents 16 to 19 years of age completed an anonymous telephone survey. Only 127/567 (22%) had been tested for HIV. Recently, the CDC reported on the rate of HIV testing among racial/ethnic minorities. The findings were based on results from the 1999 National Health Interview Survey (NHIS), an annual household based survey of U.S. non-institutionalized residents 18 years and older. The survey found that approximately 30-40% of the population had ever been tested for HIV but that less than 20% were tested in last year. Assuming that recent testing is the better proxy for rates of testing among youth, since many youth are newly sexually active, we can conclude that rates of testing among youth are low. A final indication of the low rates of HIV testing among youth comes from the surveillance data themselves. Given the total number of AIDS cases diagnosed in 1998 among 25-39 year-old women (5666) and the estimated time that it takes to develop AIDS after initial infection, the low number of youth reported with HIV during the same year (1300), suggest poor rates of HIV testing of female youth.

Specificity of HIV Surveillance Data

An advantage of local surveillance data over national data is that it often contains information about the geographic location of the infected person's residence. In some cities this information is collected at the level of the zip code or census tract, while in other

cities it is collected at the level of the street address. This information is useful for selecting neighborhoods where higher numbers of infected persons reside. However, this information may not be useful for finding HIV-infected and at-risk youth.

Few female youth residing in the neighborhoods with high rates of adolescent female HIV are in fact infected. Furthermore, evidence suggests that not all youth residing in these neighborhoods are at equal risk. This is particularly true for adolescent females, where the best estimate of neighborhood HIV prevalence was between 0.05% and 2.0%, based on data from local adolescent medicine clinics and community based organizations participating in a marketing campaign to get youth tested for HIV. In contrast, the prevalence of HIV among men who have sex with men tested at local STD clinics are greater than 20%.

Published data from the REACH study suggest that there are important behavioral differences between HIV-infected and -uninfected female youth from similar communities and similar demographic characteristics [Wilson et al. *J Adolesc Health* 2001;29 (3 Suppl):8; Vermund et al. *J Adolesc Health* 2001;29 (3 Suppl): 49]. The REACH Study was an observational study involving HIV-infected and -uninfected high risk 12-18 year-olds recruited from adolescent medicine clinics in the U.S. between 1996 and 1999. At entry, all participants completed a demographic and behavioral survey. The study found that while there were many similarities between infected and uninfected participants with regard to race and ethnicity, numbers of recent sex partners, and rates of gonorrhea and chlamydia (38% vs 35%), the HIV-infected girls were more likely to have dropped out of school (29% vs 16%) or to have older sex partners. Identifying girls at highest risk for choosing older male sex partners, particularly ones at high risk for HIV, may be very important in designing effective HIV prevention interventions for female youth.

Adolescent Trials Network (ATN) Protocol 016

Given the limitation of the current surveillance data, the ATN has developed

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and is now implementing ATN Protocol 016. A long-term goal of the two-year ATN Protocol 016 is to develop the capacity to identify, test, and enroll youth at highest risk for HIV-infection into prevention trials in several cities with high prevalences of HIV-infection, including Miami, Los Angeles, New York, Washington DC, Baltimore, and Philadelphia. The study may eventually expand to include Chicago, Boston, San Francisco, and Puerto Rico. The first phase of this protocol grew out of the growing appreciation for the limitation of current local surveillance data. The specific aims are:

1. To characterize epidemiology of adolescent/young adult STDs and HIV in each city using existing local surveillance and published data;

2. To interview community partners and HIV-infected youth from high prevalence neighborhoods to find out about community-based organizations and venues such as housing projects, schools, bars, clubs, street corners, and parks where youth at high risk communities could be recruited for HIV prevention projects;

3. To set up temporary HIV counseling, testing and referral services at selected sites to demonstrate capacity to identify infected and high risk uninfected youth. The second phase of ATN 016 will build on these partnerships to adapt interventions to local requirements and implement studies in an array of youth-focused venues.

Summary

Providing effective HIV treatment and prevention services to adolescents has emerged as a significant issue in many areas of the U.S. hard hit by HIV. Young males with same sex contact, young injection drug users, and runaway youth are all at high risk for HIV, but females appear to acquire the larger proportion of HIV as young teens, and their risk characteristics are poorly understood. A particular challenge in HIV prevention is to identify the teenage girls at highest risk for HIV acquisition and to develop and implement effective prevention interventions. ▲

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