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IDCR

INFECTIOUS DISEASES IN CORRECTIONS REPORT

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ABOUT IDCR

IDCR, a forum for correctional problem solving, targets correctional physicians, nurses, administrators, outreach workers, and case managers. Published monthly and distributed by email and fax, IDCR provides up-to-the moment information on HIV/AIDS, hepatitis, and other infectious diseases, as well as efficient ways to administer treatment in the correctional environment. Continuing Medical Education credits are provided by Medical Education Collaborative (MEC). This activity is jointly sponsored by IDCR and Medical Education Collaborative (MEC). IDCR is distributed to all members of the Society of Correctional Physicians (SCP) within the SCP publication, *CorrDocs* (www.corrdocs.org).

IDCR and AAHIVM have united to improve the quality of health care delivery in the nation's correctional facilities by leveraging the knowledge, experience and resources of two diverse and accomplished groups of HIV and correctional health care experts.

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EVERYTHING YOU WANTED TO KNOW ABOUT HIV DRUG RESISTANCE BUT WERE AFRAID TO ASK

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Introduction

Antiretroviral therapy (ART) has revolutionized the management of HIV infection. A recent analysis estimates that currently available combination ART regimens have increased the life expectancy of HIV-infected individuals by approximately 24 years.¹ The limitations of ART are plain to HIV clinicians and their patients. Although generally well tolerated, ART can be complicated by immediate and chronic adverse effects. Further, therapy is expensive and must be taken for years, if not for life. The astoundingly rapid ability of HIV to replicate and produce functional but mutated virus has presented the greatest challenge to the long-term control of the infection. In corrections, where HIV-infected inmates may pass in and out of prison and jails and have intermittent exposure to ART, HIV drug resistance is not uncommon. For correctional health providers managing HIV infection, an understanding of HIV drug resistance is essential. Below are some of the most commonly asked questions regarding ART resistance.

How common is drug resistance?

The prevalence of ART drug resistance has changed over time. Early in the epidemic, patients treated with zidovudine (AZT) or stavudine (d4T) mono-therapy quickly developed resistance to these drugs. Likewise, dual nucleoside reverse transcriptase inhibitor (NRTI) regimens used in the early 1990s also led to NRTI drug resistance, albeit at a slightly slower rate compared with mono-therapy. With the advent of protease inhibitors and use of triple combination therapy, profound reductions in HIV viremia were achieved. However, treatment failure rates, typically a consequence of suboptimal adherence to regimens requiring three times a day administration and/or large numbers of pills,

were common. In a study from the Johns Hopkins HIV clinic in Baltimore, only 37% of their patients starting their first protease inhibitor (PI) based regimen between 1996 and 1998 had HIV viral load levels below the limit of detection (500 copies/mL).² An analysis of drug resistance from this early era of potent HIV therapy found that two thirds of individuals in a representative sample of patients receiving HIV therapy in the US had HIV viremia of at least 500 copies/mL; of these 76% had evidence of drug resistant virus on testing.³

Of course, many of the patients developing resistant HIV had previously been exposed to suboptimal regimens, leading to the cultivation of drug resistance mutations of the virus that hamstrung their subsequent combination therapies. A recent study of drug resistance conducted at the HIV clinic at The University of North Carolina, found that starting therapy with a regimen that did not contain a PI or a non-nucleoside reverse transcriptase inhibitor (NNRTI) as part of a three-drug combination was a strong predictor of triple class (i.e. NRTI, NNRTI and PI) drug resistance.⁴ Interestingly, of those few patients who started on a triple drug regimen containing a PI or NNRTI but developed triple class resistance, almost all were on a PI that was not co-administered with ritonavir (i.e. unboosted PIs).

Heavy reliance on highly potent ritonavir-boosted PIs and NNRTIs as the anchors of HIV therapy has led to a profound suppression of HIV replication, hampering the development of drug resistance. Studies of ritonavir-boosted PI regimens have consistently demonstrated that virologic failure to these agents is rarely associated with resistance to the PI, but rather to the com-

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LETTER FROM THE EDITOR

Dear Corrections Colleagues,

As we reflect on the year that is slipping away, one thing is clear - it was not boring. For those of us involved with the management of infections in our prisons and jails 2006 brought much for us to consider (and lots for us at *IDCR* to cover) including the Institute of Medicine report on research in prisons, the investigation of the transmission of HIV infection within the Georgia Department of Corrections reported in the *MMWR*, new CDC recommendations on screening for HIV infection, updated guidelines on initial antiretroviral therapy, the approval of a new HIV protease inhibitor and a vaccine for human papilloma virus and the brisk spread of community acquired MRSA. All of this in addition to our usual coverage of conferences, our interviews with experts and *IDCR's* symposium at the NCCCHC conference.

The past 12 months have also seen some changes here at *IDCR*. The newsletter is now independent of Brown University. Further, we have developed close ties with the American Academy of HIV Medicine (AAHIVM), and we have expanded to include additional content with each issue. Reflecting on our achievements this year, I can only be proud of our staff, board and authors. Our Managing Editor, Elizabeth Closson, in particular, has been essential to getting the newsletter to you every month.

Since becoming Chief Editor, my goal has been to produce a newsletter readers would want to read and keep handy for future reference. The *IDCR* coverage of the management of depression in the setting of HIV, tuberculosis, hepatitis B virus and infection control are examples of issues that clinicians within and outside of corrections continue to find useful.

In this month's issue, we continue to strive to keep you informed. Our interview with the CDC's Dr. Richard Wolitski provides an indepth look at an important HIV/STD prevention trial conducted in four state prisons and highlights the challenges we continue to face in trying to reduce risky behaviors. As we increasingly rely on HIV resistance testing, we have included answers to some of the most commonly asked questions regarding drug resistance and try to un-code the mystery surrounding resistance.

At the cusp of 2007, we are working to create a line-up of issues that will continue to be useful and informative. One thing I can promise, it won't be boring.

Sincerely,

David A. Wohl, MD
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Faculty Disclosure

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panion drugs in the regimen.⁵⁻⁷ In contrast, virologic failure to NNRTI-based regimens is more likely to be accompanied by detectable resistance to the NNRTI, often in tandem with the M184V (see HIV 101) mutation that confers severely reduced susceptibility to lamivudine (3TC) and emtricitabine (FTC)⁸⁻⁹ (See Resources for link to a guide to reading HIV genotype resistance test).

Recently presented results from an AIDS Clinical Trials Group (ACTG) study in which treatment-naïve patients were assigned to 2 NRTIs plus the NNRTI efavirenz (EFV) versus 2 NRTIs plus the boosted PI lopinavir/ritonavir (LPV/r) provides some insights into the frequency of drug resistance with current ART.⁸ After 96 weeks, both of these study groups experienced high levels of virologic suppression below 50 copies/mL (89% for EFV versus 77% for LPV/r; $p = 0.003$). Study defined virologic failure (a lack of 10 fold or greater drop in viral load, virologic rebound before week 32, failure to suppress to less than 200 copies/mL after 32 weeks or rebound after week 32) was observed in 94 of the 253 subjects randomized to LPV/r + 2 NRTIs and 60 of the 250 assigned to EFV + 2 NRTIs. For the LPV/r + 2 NRTI arm, 52 of these 94 had resistance testing results available and 8 had NRTI mutations detected but none had any major PI mutations evident. In contrast, 33 of the 60 subjects on EFV + 2 NRTIs with genotype results available had one or more NRTI mutations detected and 16 (48% of those with genotypes in this arm) had NNRTI resistance.

The take-home lesson from this trial and other studies of resistance to current ART regimens is that the great majority of patients treated with ART will achieve virologic suppression. Of those who do experience virologic failure, a substantial proportion does not have drug resistance evident at the time of failure. For some of these patients, a total lack of adherence could explain this observation as the absence of drug removes the selective pressure applied by ART and permits non-resistant wild-type virus to rebound. In other cases, the presence of drug resistance appears to be influenced by the composition of the regimen, with resistance rarely detected when regimens contain a ritonavir-boosted PI.

How adherent must patients be to avoid drug resistance?

The dogma for several years has been that HIV-infected individuals receiving ART should take, at a minimum, 95% of the doses of medication prescribed. This canon of HIV management was rooted in the findings of an important study conducted in the late 1990s in a Veteran's Administration hospital in Nebraska in which adherence to HIV therapies was monitored using electronic medication bottle caps that recorded the opening of the medication bottle.¹⁰ In this study, adher-

ence at 95% or better was associated with the least risk of uncontrolled viremia with only 22% of patients at this level of adherence having a viral load >400 copies/mL compared to 61% with adherence between 80% and 95%. Lower levels of adherence were associated with even greater rates of detectable virus. It should be noted that patients in this study had varying degrees of treatment experience; for some this was the first regimen and others were highly treatment experienced. Further, in this cohort, PIs were commonly used and were not boosted with ritonavir.

The advent of boosted-PIs and the emergence of NNRTIs since this study was conducted have likely shifted the required adherence level downward as these medications achieve high concentrations in the blood plasma, have relatively long half lives, and, in the case of boosted-PIs, are relatively 'resistant' to resistance. While it remains unclear just how adherent patients need to be to the potent therapies now available, there is some evidence that rates of virologic failure to these therapies can be low even when adherence falls below 90-95%. Provocative work by David Bangsberg and colleagues at UCSF suggests that adherence to our current first line therapies may not need to be absolutely in the range of 90%-100% for these regimens to achieve and maintain viral suppression. In his studies of a cohort of marginally housed HIV-infected men and women in San Francisco, he found that the risk of resistance to NNRTI-based regimens increased only when adherence dropped to below 54%.¹¹ Above this level of adherence, the overwhelming majority of patients had viral loads of < 400 copies/mL. With unboosted-PI-based therapy, a more linear relationship between adherence and suppression of viral replication, as described by the VA group in Nebraska, was observed, with viral suppression inversely proportional to adherence level. Modeling data suggest that adherence to regimens with the potency of ritonavir-boosted PIs should produce similar resistance rates as seen for NNRTIs.¹²

This does not mean that patients should not be encouraged to take all their medications as directed. Patients should continue to be encouraged to take their medications exactly as directed. The San Francisco study results have yet to be replicated by others. Further, the study used 400 copies/mL as a threshold for undetectable rather than 50 copies/mL and low level virus may increase risk of resistance development over time. Individual variability in drug metabolism and other factors may make it dangerous to apply the aggregate data from this particular investigation to a patient. However, at the same time clinicians should appreciate that the 90%-95% adherence threshold we have held our patients to may no longer be justified when NNRTI- or ritonavir-boosted PI-based therapies are used in patients with susceptible virus. This is important when considering the administration of punitive responses to ART adherence levels that are

below 90%. In some prisons and jails, adherence below a certain level may lead to treatment discontinuation. While the rationale for such an approach is sound, the adherence threshold chosen may need to be less rigid and reflect the available data on current potent ART regimens. These data suggest a more accurate level may be lower than 95% for NNRTIs and probably for boosted PI-containing regimens.

The genotype says there is no resistance. Can I be sure of that?

HIV drug resistance tests have been incredibly useful to clinicians managing HIV infection. However, as with any tool or test, it is important for the user to understand their limitations (See Resources for link to a comparison of HIV resistance test).

HIV resistance tests can detect a drug resistant virus that is present in sufficient numbers. If a resistant viral strain exists in very low numbers, the tests will likely miss it. Therefore, resistance can be present at low levels and not be picked up by the resistance tests. This is more likely to happen in several situations. For example, sometimes a resistance test is performed when there is very little virus around (i.e. a viral load of 1,000 copies/mL or less). As the overall amount of virus is low, the HIV drawn into the sample for testing may not be very representative of the viral population present in the circulation and resistant mutants may have been missed. Similarly, when a patient has developed drug resistance and then stops their medication, the wild-type (not drug resistant) virus re-emerges as it can now replicate freely with the removal of the HIV drugs. As the wild-type grows, it dilutes the population of the resistant virus, making it harder to detect. Importantly, even though the wild-type increases to great numbers, the resistant virus is not gone but continues to be present in low numbers and, under the right conditions, such as re-application of the HIV medications, can be selected to grow preferentially. It is currently believed that once a resistant virus is cultivated, it never disappears, but poses a lingering threat to the responses to future ART.

How often do people get infected with drug resistant virus?

The answer to this question depends on where the person with HIV is infected. In major cities of the US and Europe, anywhere between 10-25% of people acquiring HIV are infected with HIV that is resistant to at least one HIV drug.¹³⁻¹⁸ In all studies, resistance is highest among the ART drug classes to NRTIs and increasingly to NNRTIs, followed by PIs. Data from New York, which may well represent a worst-case scenario, found an increase over time in acquired ART resistance among 361 individuals with acute or recent HIV infection diagnosed between 1995-2003.¹⁴ Comparing the periods of 1995-1998 and

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2003-2004, rates of ART resistance increased from 13% to over 24%. NRTI resistance was the most prevalent but was relatively stable. PI resistance was fairly uncommon (1.3%) in the earlier period but rose to 7.1% of patients in the more recent period - a trend that did not reach statistical significance. For NNRTIs, resistance paralleled their popularity with a significant rise from 2.6% to more than 13%. Other studies of recently infected patients in other locations generally report a slightly lower prevalence of drug resistance than found in this study.

Studies of drug resistance in chronically infected but treatment-naïve patients have also been reported.^{13,17} In one study of 491 patients under care in 25 US cities from 1999-2001, 11% had at least one ART resistance mutation detected.¹³ Most of the mutations detected were those that reduce susceptibility to the NRTIs, especially the thymidine analogues and 3TC/FTC.

The rate of transmitted drug-resistance in non-metropolitan areas such as rural regions of the US South - where most people with HIV infection in this country live - is not clear. What has become evident is that acquired drug resistance has ramifications for subsequent treatment success. Several studies have observed increased rates of treatment failure in patients with pre-therapy resistance.¹⁹⁻²² Although wild-type virus may be able to out-compete resistant mutants, some resistance mutations can persist at levels that permit long-term detection by resistance assays; mutations conferring resistance to all three of the initial ART classes have been described in chronically infected, treatment-naïve patients. For these reasons, the US Department of Health and Human Services (DHHS) guidelines on initial therapy of HIV infection, updated in October 2006, recommend genotype resistance testing be performed in all treatment naïve patients prior to initiation of HIV therapy.²³

What does it mean when someone says that resistant virus is "less fit"?

In vitro studies and some clinical trials suggest that certain mutations of HIV in response to drug therapy may reduce the pathogenicity of the virus.²⁴⁻²⁶ To understand how resistance can impact the ability of the virus to replicate it is helpful to consider the dynamics of HIV replication in terms of basic Darwinian evolution. Within the body of an HIV-infected individual ART selects for mutated virus that can survive in a milieu includes these drugs. Continued pressure by the ART favors the persistence of such drug resistant virus. However, in many types of drug resistant mutations the virus evolves to evade the effects of drug

therapy but comes with a cost to their ability to replicate relative to wild-type virus. That is, drug resistant virus, in becoming mutated, may not work as well as virus that does not contain drug resistance mutations.

In some cases, the reduced fitness of resistant virus can be exploited during therapy to slow the pace of disease progression. Specifically, in cases where there are few antiretrovirals to which the virus remains susceptible the continued use of certain agents to which the patient's virus is known to be resistant may be used to maintain levels of the relatively less 'fit' resistant virus. The best example of this effect is found in the M184V resistance mutation. This mutation essentially neutralizes any antiviral activity of 3TC and FTC. However, this mutation has been reported to inhibit the ability of the virus to replicate and may sensitize resistance virus to the effects of AZT and tenofovir. In one study, patients failing 3TC-containing therapy with a M184V mutation were randomized to continue their 3TC alone as mono-therapy or stop all ART.²⁷ Those that continued on 3TC alone had a truncated rise in HIV viral load and reduced declines in CD4 cell counts compared to those who were no longer taking ART. Thus, continued 3TC had some effect on viral replication even though the M184V mutation was evident. Some clinicians take advantage of this phenomenon and maintain 3TC or FTC as part of salvage regimens in patients with drug resistance that includes the M184V mutant.

Whether resistance to other antiretrovirals can yield similar effects on fitness is being studied. There is some evidence that resistance to the thymidine analogues (AZT and stavudine), as well as the K65R mutation that can be selected for during therapy with tenofovir as well as some NRTIs, have a detrimental effect on viral fitness. What is clear though, is that it is probably not wise to maintain an NNRTI when resistance to this class of drugs is detected. Unlike the major NRTI mutations and the constellation of mutations that are usually needed to reduce susceptibility to the PIs, the primary NNRTI mutations seem to have less of an effect on the replication ability of HIV. This may explain why the K103N NNRTI mutation can remain detectable by genotype resistance testing long after NNRTI exposure. Further, early clinical trial data of a second generation NNRTI, etravirine (TMC-125), indicate reduced response to this new agent with an accumulation of NNRTI resistance mutations.²⁸ The bottom line is that, in general, maintaining NNRTI therapy in the face of documented NNRTI resistance mutations should not be done. This is not to say that continued therapy with a PI or NRTI could not also lead to the accumulation of additional mutations once resistance has developed. It can, and continuation of any ART to which the virus is resistant has to be considered very carefully when effective treatment remains available.

What is the best way to manage patients who have developed resistance to many drugs and ART classes?

The best way to manage resistance is introduction of drugs to which additional resistance has not developed. A number of new drugs in new classes are being developed and are expected to become available to patients within the next two to five years. These include inhibitors of the HIV integrase enzyme and the processes that lead to viral maturation within a CD4 cell, blockers of the CCR5 co-receptor and the CD4 receptor, as well as new drugs in existing classes. In addition, there are recently approved antiretrovirals that have activity against certain types of resistant virus that can be employed to craft a new regimen when a prior combination fails.

Whether using new novel agents, existing drugs, or recycling previously used regimens to which the virus is not considered to have resistance, the principle remains the same: use as many drugs in the new regimen as possible that have activity against the virus that exists in that patient. Studies of new antiretrovirals in treatment-experienced patients have consistently demonstrated that when these drugs are coupled with agents to which the virus remains susceptible, response to therapy is better.²⁹⁻³¹

We are approaching a critical mass of potent therapies that can be used in such salvage regimens. With the approvals of the tipranavir and darunavir - PIs that are boosted with ritonavir and have activity against many strains of virus resistant to other PIs - plus the availability of enfuvirtide (T-20), new regimens that offer a reasonable chance of success can be devised. Studies of both of these PIs demonstrate unprecedented responses in treatment-experienced patients, especially when used with other active drugs.²⁹⁻³¹

Etravirine, the next generation NNRTI; MK-0518, the first HIV integrase inhibitor and maraviroc, a CCR5 inhibitor are all offered via expanded access programs. While these therapies will remain out of reach for most correctional facilities until FDA approval, they offer the promise of effective agents that, when available, can complete an attractive salvage regimen. For this reason, patients with multiple drug resistant virus may be best managed, when possible, by a delay in a change of therapy until one or more of these new agents becomes available.

Other than counseling my patient regarding adherence what else can I do to reduce the risk of HIV drug resistance?

While it is ultimately the patient's responsibility to take his or her medication, the clinician must choose regimens that are sound and are most likely to provide long-term

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viral suppression. Initial therapy should be prescribed with the goal of long-term viral suppression. There are antiretroviral regimens that have been found to be less effective than the currently recommended first-line therapies. Some, like the fixed dose combination of abacavir, 3TC and AZT have been found to be suboptimal compared to preferred regimens. Other combinations have been found to be outright dangerous (e.g. all other triple NRTI regimens except, perhaps, tenofovir + 3TC or FTC + AZT) and should never be prescribed. The US DHHS recommendation for ART for adults and adolescents is a user-friendly guide to initial therapy and lists clearly the preferred regimens, alternatives for special cases and completely contraindicated combinations.²³ Unless there is an extremely compelling rationale, the drugs listed in the preferred regimens should be used in all cases of initial HIV therapy.

Baseline genotypic resistance testing prior to the start of HIV therapy is becoming less and less optional. The guidelines are clear on the utility of this test in reducing downstream problems for patients and a recent analysis suggests such testing is cost-effective.²³ Detecting transmitted resistance or mutations that may linger from prior ART exposure can help guide proper treatment during the incarceration and after release. The price of the genotype resistance assays has come down, making cost less of a justification for ignoring the DHHS recommendations.

HIV clinicians have become accustomed to evaluating HIV-infected patients every three to four months. However, clinicians must be attuned to the development of changes in the viral load that may signal the emergence of drug resistance and act on these data prior to the next patient visit. Unexpected changes in viral load should prompt immediate reevaluation of the

patient and the drawing of a genotype resistance test. At the North Carolina Department of Corrections, we are able to order a genotype and if the viral load is undetectable, the genotype is not run by the commercial laboratory - thus, avoiding unnecessary billing. Prompt action can prevent further cultivation of resistance that can handicap future treatment options.

For patients new to the system, the greatest challenge can be determining what therapies they have been exposed to in the past.


As tiresome as it is, obtaining a release of information and old records from outside providers can ultimately be time- and money-saving. In cases where little can be learned about the prior ART history, restart of the last regimen (if it is not some bizarre combination) can be attempted with a genotype obtained after two to four weeks to detect major resistance mutations that may lead to the overhaul of this regimen. So as not to perpetuate the 'black box' of HIV treatment history, inmates should be given a record of their medications prior to release. Wallet-sized cards that can list HIV medications and other essential clinical data are available from at least two pharmaceutical companies. 'Home-made' version created by corrections staff can work equally as well. When possible, a listing of the major ART resistance mutations should be added to these cards for the benefit of the patient's future providers.

Lastly, salvage regimens should be created with considerable thought. Salvage HIV therapy generally yields diminishing returns with each subsequent combination less likely to be effective compared to the previous. New therapies may help increase the odds of treatment success beyond initial therapy but, it continues to be imperative that active agents not be wasted by being included in regimens that are predicted to be impotent based on resistance or patient history (i.e. if the patient was on AZT mono-

therapy for six years in the 1980s, it is safe to assume they are resistant to this medication even if the resistance test does not detect AZT associated mutations). There should be a low threshold for consultation with an HIV expert when considering the management of the treatment-experienced patient. Outreach to such experts in the community, at academic medical centers or other correctional facilities should be sought and lines of communication established.

Summary

Resistance happens. However, resistance to HIV medications need not be inevitable. Potent therapies are now available in extremely convenient formulations and dosing schedules. Adherence remains a cornerstone of drug resistance prevention and correctional facilities have unique advantages in the monitoring and encouragement of treatment adherence. In addition, close surveillance of response to HIV therapy and quick action when viral load increases are detected can forestall further damage from evolving mutations. New drugs in existing classes that are already FDA approved and those expected to be shortly, hold the promise of a new chance for many patients who have developed HIV drug resistance. Wise use of these medications based on clinical trials data, patient history and detected and suspected ART resistance will increase the odds for treatment success.



Go to www.AAHIVM.org to learn about membership, continuing education and the new partnership with IDCR

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Continued on page 6

HIV DRUG RESISTANCE...

(continued from page 5)

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IDCR-O-GRAM

2006 DHHS Guidelines for the Utilization of Drug Resistance Testing in Clinical Practice

- HIV drug resistance testing is recommended for persons with acute HIV infection if the decision is made to initiate therapy at this time (BIII). If therapy is deferred, resistance testing at this time should still be considered (CIII).
- Drug resistance testing is also recommended for persons with chronic HIV infection prior to initiation of therapy (BIII). Earlier testing may be considered (CIII).
- A genotypic assay is generally preferred for antiretroviral-naïve persons (BIII).
- HIV drug resistance testing should be preformed to assist in selecting active drugs when changing antiretroviral regimens in cases of virologic failure (BII).
- HIV drug resistance testing should also be considered when managing suboptimal viral load reduction (BIII).
- Drug resistance testing in the setting of virologic failure should be preformed while the patient is taking his/her antiretroviral drugs, or immediately (i.e., within 4 weeks) after discontinuing therapy (BII).
- Drug resistance testing is not advised for persons with viral load <1,000 copies/mL, because amplification of the virus is unreliable (DIII).

Rating Scheme for Recommendations

Strength of Recommendation: A= Strong B= Moderate C= Optional D= Should usually not be offered E= Should never be offered

Quality of Evidence for Recommendation: I= At least one randomized trial with clinical results II: Clinical trials with laboratory results III: Expert opinion

Source: The US Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. October 2006. Available at <http://aidsinfo.nih.gov>.

SPOTLIGHT - INTERVENTIONS TO REDUCE HIV AND STD TRANSMISSION RISK BEHAVIORS FOLLOWING PRISON RELEASE - A CONVERSATION WITH DR. RICHARD WOLITSKI

The results of the START Study, a randomized controlled trial of interventions to reduce HIV/STD risk behaviors among 522 young men being released from prison in four states (California, Mississippi, Rhode Island and Wisconsin), were recently published in the American Journal of Public Health. IDCR Chief Editor, Dr. David Wohl, spoke with Dr. Richard Wolitski, lead author of the study, which was supported by the Centers for Disease Control and Prevention (CDC). Dr. Wolitski is the Acting Deputy Director for Behavioral and Social Sciences in the CDC's Division of HIV/AIDS Prevention.

David Wohl (DW): You led what many consider to be a very important and unique study looking at reducing HIV and STD risk behaviors among young men released from prison. Could describe the two interventions that were studied?

Richard Wolitski (RW): The Project START intervention was collaboratively developed by researchers at the four sites and CDC. It compared the relative efficacy of two different interventions. The first intervention was a single-session intervention that was conducted before participants were released from prison. The single-session intervention was based on a brief HIV risk assessment and risk-reduction planning intervention developed by Grinstead and colleagues that had previously been shown to reduce risk in this population. We compared the effects of the single-session intervention with those of the six-session enhanced intervention.

The enhanced intervention was meant to provide a bridge between incarceration and then reintegration into the community. The enhanced intervention had two sessions that were conducted before participants were released. The first of these was identical to the single-session intervention, and the second session focused more broadly on the individual participant's needs after release. It included an assessment of needs and planning for housing, employment, financial problems, social relationships, and avoiding reincarceration. Then participants had four additional scheduled interventions after release. These interventions were client-centered and adopted elements of prevention case management and motivational interviewing.

DW: When I think about that kind of case management and a client-driven approach, I would think that there might be some variability in the frequency with which case managers, following release, would interact with participants. Was there any freedom on the part of the case managers in the enhanced intervention or were they restricted to only four sessions with the participant after release?

RW: All the participants were scheduled to receive four scheduled interventions, but we

also made it possible for the participants to receive additional sessions as needed during the three-month intervention period following release. There weren't that many people who received additional sessions. There were a total of just 91 additional enhanced intervention sessions that were delivered to 49 participants, and most of those, 61%, received only one additional session.

DW: What were the main results of the study?

RW: The enhanced intervention was associated with a significant overall reduction in sexual risk behaviors 24 weeks after release. More specifically, we found that men who received the enhanced intervention were significantly less likely to report unprotected sex the last time they had sex and during the full recall period. Although there was a significant overall reduction in sexual risk, this reduction was due almost entirely to reductions in risk with the participants' main or primary partners.

"These interventions were guided by a harm-reduction philosophy that focused on goals that were developed by the participants and it was grounded in a holistic approach that addressed the men's reintegration needs, such as competing needs related to employment, housing, substance abuse and legal issues."

DW: There are few studies that have shown positive changes in risk behavior in general, and certainly there remains very limited data about interventions for an incarcerated or recently incarcerated population. However, I was surprised that we did not see greater differences at week 12 - at the end of the enhanced intervention. The only significant difference was seen at week 24, which is three months after the intervention was completed. Any thoughts about why you saw a greater effect after the intervention ceases?

RW: That's a really good question. One thing that's important to keep in mind is that at the 12-week interview, the participants were asked about their risk behavior since their first week of release from prison. The period of time that participants are reporting on includes a time period where enhanced intervention participants had received very little of the intervention, so it's really only at the 24-week assessment that we can look at behavior change after participants had a chance to receive the full intervention.

DW: You mentioned that the enhanced intervention seemed to motivate participants to

practice safer sex with their main partners, more so than non-main partners, and studies of HIV-infected releasees have shown that HIV-infected former inmates are more likely to practice unsafe sex with their main partner, with whom they may feel more comfortable with than casual partners. The finding that the intervention seemed to work more so with the main partners seems particularly significant.

RW: One of the things to understand about this population is that many of the men had already reduced their risk with their non-main partners and that the highest levels of risk were observed with main partners. So, I think in part what's happening here is that the enhanced intervention sensitized men to the potential risks of contracting HIV or another sexually transmitted infection from their main partners or also sensitized them to the possibility that they might be putting their main partner at risk. Many of these main partners were also at risk --- one third of the men who had a main partner believed that this partner had one or more risk factors for HIV, hepatitis or other sexually transmitted infection.

DW: Are there any plans to evaluate longer-term differences between the study arms, beyond week 24?

RW: At this time, we don't have any plans to do that. However, the CDC is supporting the packaging of the Project START intervention for dissemination to the CDC's prevention partners. This means that there will be additional opportunities to evaluate the effectiveness of this intervention as it is being delivered by local agencies.

DW: Do you think, given what you now know from looking closely at the results, that a three-month post-release intervention is sufficient?

RW: A three-month post-intervention follow-up is an acceptable standard in the field, and this follow-up is longer than others that have been used in HIV prevention studies with incarcerated men. Certainly, having a longer follow-up is better, but it requires additional resources that were not available for this study. It's possible that, given the comprehensive nature of this intervention, some of the participants established a stable pattern of behaviors that allowed them to maintain reduced risk behaviors over time. But we really don't know that at this point in time.

DW: The results that you found at week 24 after release were significant, but 68% of those receiving the enhanced intervention reported unsafe risk behaviors, albeit versus 78% of those in the single session arm. How could anyone get excited about over

Continued on page 8

two thirds of the people in the enhanced intervention still practicing risky behavior?

RW: We have to be realistic about what any one intervention can accomplish. A lot of people would have thought that it would be difficult or impossible to see any risk reduction in this population. As you know, incarcerated men are sometimes viewed as people who really don't care about their own health or the health of their partners, and this study demonstrates that it is actually possible to motivate these men to reduce their risk behavior. It does indicate, though, that there is a need for additional intervention for some men, or perhaps different types of intervention for men who did not respond to this particular intervention.

DW: Your study concentrated on people following release, and a common misperception, is that HIV-infected people in prison acquire their infection during incarceration. The CDC took a lead with a study of an outbreak of acute or transmitted HIV within a correctional system in Georgia. Your study focused on people getting out of prison, versus an intervention to try to reduce acquisition of HIV within a correctional system. Why?

RW: One thing that is important to keep in mind is that incarcerated men continue to be part of the communities that they came from, and that most men who are incarcerated will be re-released back into the community. Addressing this period of transition from incarceration to release is really critical for public health. We chose to focus on this period after release in part because we

wanted to design an intervention that would be feasible for health departments or community-based organizations to implement in collaboration with local correctional facilities. So our primary interest here was driven by the types of organizations that we thought might be implementing this intervention in the future.

DW: Right. In your conclusion to the paper you call upon community-based organizations and health departments to work in tandem with correctional institutions to improve the well-being of people such as those who enrolled in your study. Given what you've learned and your experience, what do you see as being obstacles to that kind of cooperation and how your results might help us to overcome them?

RW: The most important thing that this study shows is that this type of intervention is feasible and can be efficacious in reducing risk behavior among incarcerated young men. There are a number of challenges that people face when coming from outside correctional settings and trying to conduct this type of intervention, and one of the biggest challenges is gaining entry into the facilities. What we hope is that this paper and this study will give health departments and community-based organizations that are interested in establishing those relationships with correctional facilities a model that they can show to local correctional facilities to show that this can work.

DW: You mentioned earlier that the intervention is going to be packaged and become more accessible. Any details about

how those who are interested in learning more about the program can get the materials to actually start to implement their version?

RW: Probably the best thing that I could do is to refer people to the CDC website (www.cdc.gov/hiv/PROJECTS/ProjectSTART), where there is additional information that is online about the study. The actual intervention package will not be available for another year or two, from the CDC. Some of the local researchers may be willing to provide additional information in the interim, but readers would have to contact them directly. The contact information for all principal investigators is listed on the Project START website.

DW: So, summing-up, the take-home lessons from the START Study seem to be that, even in this difficult-to-reach and difficult-to-change population, you can see some change in risky behavior in a positive direction, and while this is encouraging, the results certainly points to the need for further development of interventions to complement this one. Is that fair to say? Is there anything more you'd say to expand upon that?

RW: I think that's a good summarization of the study, and I would say that Project START can be an important part of a comprehensive strategy for reducing HIV transmission among incarcerated men and their sex partners. Other elements of that approach include HIV testing upon entry and release from prison, as well as interventions that are designed specifically for persons living with HIV and AIDS.

RESOURCES

Slides from the NCCHC Pre-conference Seminar Infectious Diseases in Corrections: An Expert Panel
October 28, 2006
<http://www.idcronline.org/archives.html>

Federal Bureau of Prisons Clinical Practice Guidelines
<http://www.bop.gov/news/medresources.jsp>

Department of Health and Human Services 2006 Adult and Adolescent Antiretroviral Treatment Guidelines
<http://www.aidsinfo.nih.gov/guidelines/>

International AIDS Society-USA Panel 2006 Recommendations of the Treatment for Adult HIV Infection
<http://jama.ama-assn.org/cgi/content/full/296/7/827>

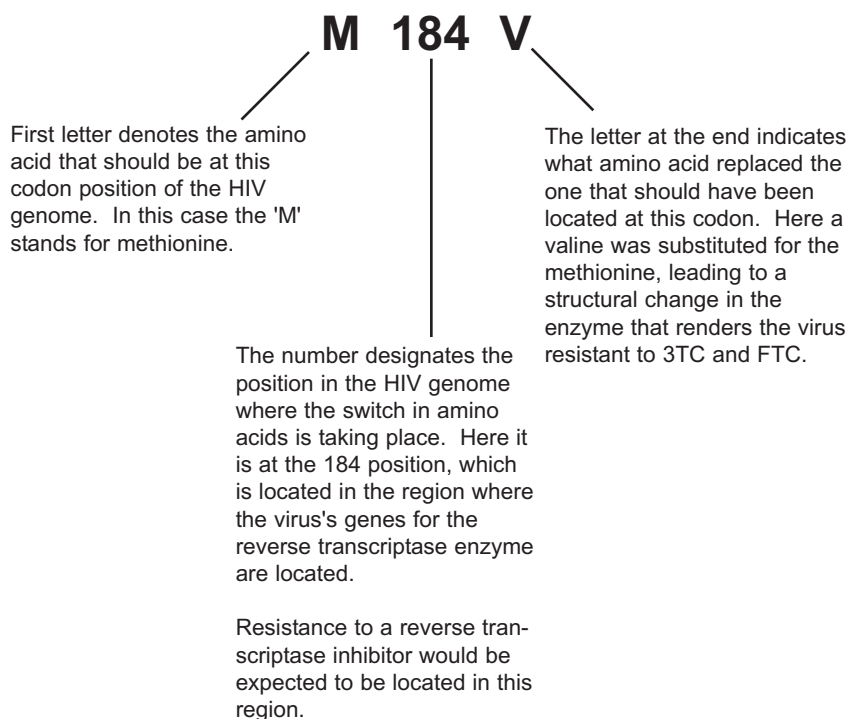
CDC's Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings
<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm>

Genotype and Phenotype Resistance Tests Compared
www.thebody.com/nmai/pdfs/resistance.pdf

A Guide To Resistance and Reading Resistance Tests
www.thebody.com/resistance/pdfs/resistance.pdf

HIV 101

The Anatomy of an Antiretroviral Resistance Mutation



SAVE THE DATES

American Correctional Association Winter Conference
Tampa, FL
January 19-24, 2007
Visit: www.aca.org/conferences/winter07/

2007 National African American MSM Leadership Conference on HIV/AIDS: "Brothers, It's Our Time"
Charlotte, NC
January 25-28, 2007
Visit: www.aesmonline.com/Conference.htm

The 2nd National Conference on Methamphetamine, HIV, and Hepatitis
Salt Lake City, UT
February 1-3, 2007
Visit: www.xmission.com/~uhrmeth/registration.php

2007 National Conference on African-Americans and AIDS Featuring the Rev. Jesse L. Jackson
Philadelphia, PA
February 12-13, 2007
Visit: www.minority-healthcare.com

14th Annual Ryan White National Youth Conference on HIV and AIDS
Oakland, CA
February 17-19, 2007
Visit: www.napwa.org/rwnyc/index.html

14th Conference on Retroviruses and Opportunistic Infections
Los Angeles, CA
February 25-28, 2007
Visit: www.retroconference.org/2007/

Interferon and Ribavirin in Hepatitis C Virus Infection: Mechanisms of Response and Non-Response
Chicago, IL
March 1-3, 2007
Visit: www.aasld.org/eweb/DynamicPage.aspx?webcode=07_hepatitisctc

Academic and Health Policy Conference on Correctional Health
Sponsored by the University of Massachusetts Medical School and UMass Correctional Health
Boston, MA
March 29-30, 2007
Visit: www.umassmed.edu/commedinterior.aspx?id=33110

16th Annual HIV Conference of the Florida/Caribbean AIDS Education and Training Center
Orlando, FL
March 30-31, 2007
Visit: www.factc.org/Conference/

Updates in Correctional Health Care
Orlando, FL
May 5-8, 2007
Visit: www.ncchc.org/education/index.html

IAS 2007: 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention
Sydney, Australia
July 22-27, 2007
Visit: www.ias2007.org/start.aspx

NEWS AND LITERATURE REVIEWS

Sexual Violence Inside Prisons

Given the many associated public health consequences of sexual violence, Wolfe et al. conducted a study to estimate the prevalence of sexual victimization within an unidentified state prison system. The weighted estimates, which were constructed by gender and facility size, show that rates of inmate-on-inmate sexual victimization, defined as either abusive sexual contact (intentional touching of specified areas of the body) or nonconsensual sex acts (forced sex acts, including oral and anal sex), in the previous six months were highest for female inmates (212 per 1,000), more than four times higher than the rates for males (43 per 1,000). Additionally, abusive sexual conduct, was more likely between inmates and between staff and inmates than nonconsensual sexual acts, such as rape. These results were based on an audio-computer assisted interviews administered to 6,964 male and 564 female inmates housed in the twelve prison facilities. Extrapolating from the estimates, the authors suggest that the number of potential victims susceptible to HIV and other health consequences of sexual victimization could be as high as 22,000 male and over 3,200 female inmates on a national level. These staggering numbers underscore the need for targeted interventions to reduce this level of abuse.

Sexual Violence Inside Prisons: Rates and Victimization. Wolff, N et al. *Journal of Urban Health.* 2006;83(5):835-48.

Incarceration as Forced Migration: Effects on Selected Community Health Outcomes

Researchers at the University of North Carolina, utilizing data from each of the 100 counties in that state, found that county rates of sexually transmitted infections (STI) and teenage pregnancies consistently increased with increasing incarceration rates. Thomas and Torrone obtained the results, which are published in the *American Journal of Public Health*, by calculating the correlation between rates of incarceration in state prisons and county jails and rates of STIs and teenage pregnancies during the period of 1995 to 2002. The authors use the strong associations, especially between teenage pregnancy and the most common STIs, to propose that high incarceration rates have the unintended consequence of destabilizing communities and contributing to adverse health outcomes. Specifically, they note that fewer than one half of one percent of reported gonorrhea and chlamydial infections in 2000 were reported in correctional facilities, suggesting that many of the adverse effects are felt most strongly in the community, rather than the prison. The high rates of incarceration, the authors state, create a situation of "forced migration", not unlike that found in South Africa in the late 1930's, greatly altering gender ratios, which have been shown to affect rates of teenage pregnancy, and STIs such as syphilis, and gonorrhea. Despite the correlation, the authors do not believe that the negative community health affects alone will create a dramatic policy shift regarding alternatives to incarceration.

Incarceration as Forced Migration: Effects on Selected Community Health Outcomes. Thomas, JC et al. *American Journal of Public Health.* 2006;96(10):1762-65.

Chlamydia trachomatis and Neisseria gonorrhoeae Infections Among Men and Women Entering California Prisons

Due to the limited amount of information regarding the prevalence of bacterial STI infection in prison based settings, Bernstein et al set out to estimate the prevalence of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* among newly arrived inmates at six California prisons. The cross sectional study of 698 men aged 18 to 25 years and 572 women aged 18 years and older revealed a high prevalence of *C. trachomatis* in both groups. Among men aged 18 to 25, the overall prevalence was 9.9%, while women of the same age exhibited a prevalence of 8.9%. The prevalence among all women was 3.3%. In contrast, only three cases of *N. gonorrhoeae* were detected with an overall prevalence of 0.24%, which was consistent with recent findings from other settings. The study of men was limited to an examination of those between the ages of 18-25, and given the high prevalence among this group, further study of all men entering prison may be justified. Despite the limitations, the authors suggest that the high prevalence of *C. trachomatis* infection, especially among young female and male inmates, supports routine screening upon entry into prison. Furthermore, the authors assert that screening in a jail setting, prior to entry into prison, may represent an excellent opportunity to identify and treat these infections, thus preventing complications and the burden of infection among this high-risk population.

Chlamydia trachomatis and Neisseria gonorrhoeae Infections Among Men and Women Entering California Prisons. Bernstein, KT et al. *American Journal of Public Health.* 2006;96(10):1862-66.

Implementing a Routine, Voluntary HIV Testing Program in a Massachusetts County Prison

Working within a Massachusetts county jail, researchers found that the implementation of a routine, voluntary HIV testing program resulted in a significant increase in testing rates among inmates. The study, published in the *Journal of Urban Health*, details the program in which inmates were provided group counseling and then offered private HIV testing. Among the group receiving intervention, 73.1% (734 of 1,004) of eligible inmates accepted testing, compared to 18.0% (318 of 1,723) of inmates in the control group, receiving only inmate or physician requested testing. The most commonly cited reason for refusal in the study group was "tested in the prior year" (47.5%), followed by "not at risk" (29.4%). These results indicate a higher level of acceptance than previous studies of correctional HIV testing, due perhaps, the authors suggest, to improvements in HIV treatment or testing a population with a high background testing rate. Of the study group, 457 or 45.5% had been tested for HIV in prior years, most receiving their last test within a prison setting (78.2%). While cautioning against over-testing and redundancy among inmates, the authors use their results to emphasize that routine HIV counseling, testing, and referral is acceptable to inmates and results in high rates of testing.

Implementing a Routine, Voluntary HIV Testing Program in a Massachusetts County Prison. Liddicoat, RV et al. *Journal of Urban Health.* Published ahead of print.

SELF-ASSESSMENT TEST FOR CONTINUING MEDICAL EDUCATION CREDIT

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for continuing Medical Education through the joint sponsorship of Medical Education Collaborative, Inc. (MEC) and IDCR. MEC is accredited by the ACCME to provide continuing medical education for physicians.

Medical Education Collaborative designates this educational activity for a maximum of 1.3 AMA PRA Category 1 Credit(s)TM. Physicians should only claim credit commensurate with the extent of their participation in the activity. Statements of credit will be mailed within 6 to 8 weeks following the program.

Objectives:

- The learner will be able to describe the prevalence of acquired HIV drug resistance.
- The learner will become familiar with the concept of reduced viral fitness of resistant HIV virus
- The learner will understand the design and results of the recent U.S. Centers for Disease Control and Prevention trial of interventions to reduce HIV/STD risk behaviors among young men released from prison.

- | | |
|---|---|
| <p>1. All of the following statements regarding transmitted HIV drug resistance are true EXCEPT:</p> <p>A. In studies of acutely and recently infected patients, transmitted HIV drug resistance has been found in less than 5% of patients</p> <p>B. Transmitted HIV drug resistance has increased since the mid-1990s.</p> <p>C. Resistance to the non-nucleoside reverse transcriptase inhibitors (NNRTIs) is the most common HIV drug resistance seen in recently infected patients.</p> <p>D. None of the above</p> <p>2. In the AIDS Clinical Trials Group (ACTG) study A5142 of treatment naïve patients, at 96 weeks:</p> <p>A. Almost half of those assigned efavirenz plus two nucleosides who had genotype resistance testing results available had NNRTI resistance detected</p> <p>B. Resistance to lopinavir was not seen in those patients assigned to this drug and who had genotype resistance testing results available</p> <p>C. The overwhelming majority of patients assigned to efavirenz or lopinavir/ritonavir plus 2 nucleosides had HIV viral loads below 50 copies/mL/</p> <p>D. All the above</p> <p>3. Treatment guidelines issued by the US Department of Health</p> | <p>Human Services for the initial treatment of HIV infected adolescents and adults recommends that HIV genotype resistance testing should be performed:</p> <p>A. In chronically infected patients initiating HIV therapy</p> <p>B. In patients with acute infection starting HIV therapy</p> <p>C. When virologic failure develops during HIV therapy</p> <p>D. All the above</p> <p>4. In the CDC study of interventions to reduce HIV risk behaviors among young men being released from prison at week 24 after release:</p> <p>A. Neither the enhance or the single-session intervention was found to reduce risk behavior</p> <p>B. Surprisingly, those assigned the single-session intervention reported less risk behaviors than those receiving the enhanced intervention</p> <p>C. The enhanced intervention was found to reduce risk behaviors of participants mostly with their participants main partner rather than casual partners.</p> <p>D. All the above</p> <p>5. Resistance to an HIV medication that develops during therapy remains present in the body after the medication is discontinued even though resistance testing may indicate otherwise (TRUE or FALSE)?</p> |
|---|---|

In order to receive credit, participants must score at least a 70% on the post test and submit it along with the credit application and evaluation form to the address/fax number indicated. Statements of credit will be mailed within 6-8 weeks following the program.

Instructions:

- Applications for Credit will be accepted until December 30, 2007.
- Late applications will not be accepted.
- Please anticipate 6-8 weeks to receive your certificate.



Please print clearly as illegible applications will result in a delay.

Name: _____ Profession: _____

License #: _____ State of License: _____

Address: _____

City: _____ State: _____ Zip: _____ Telephone: _____

Please Check which credit you are requesting ACCME or Non Physicians

I certify that I participated in IDCR monograph - December 2006 Issue

Please fill in the number of actual hours that you attended this activity.

Date of participation: _____

Number of Hours (max. 1.3): _____

Signature: _____

Please Submit Completed Application to:

Medical Education Collaborative
 651 Corporate Circle, Suite 104, Golden CO 80401
 Phone: 303-420-3252 FAX: 303-420-3259
 For questions regarding the accreditation of this activity, please call 303-420-3252

COURSE EVALUATION

I. Please evaluate this educational activity by checking the appropriate box:

Activity Evaluation					
	<i>Excellent</i>	<i>Very Good</i>	<i>Good</i>	<i>Fair</i>	<i>Poor</i>
Faculty					
Content					
How well did this activity avoid commercial bias and present content that was fair and balanced?					
What is the likelihood you will change the way you practice based on what you learned in this activity?					
Overall, how would you rate this activity?					

II. Course Objectives

Were the following overall course objectives met? At the conclusion of this presentation, are you able to:

- | | | | |
|--|------------|-----------|-----------------|
| • The learner will be able to describe the prevalence of acquired HIV drug resistance. | YES | NO | SOMEWHAT |
| • The learner will become familiar with the concept of reduced viral fitness of resistant HIV virus | YES | NO | SOMEWHAT |
| • The learner will understand the design and results of the recent U.S. Centers for Disease Control and Prevention trial of interventions to reduce HIV/STD risk behaviors among young men released from prison. | YES | NO | SOMEWHAT |

III. Additional Questions

a. Suggested topics and/or speakers you would like for future activities.

b. Additional Comments
