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The estimated time to complete this educational activity: 1 hour.

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GOAL

To provide the latest information in HIV medicine to enable clinicians to provide state-of-the-art clinical care to their patients with AIDS or HIV infection.

TARGET AUDIENCE

This activity is designed for HIV clinical care providers; no prerequisites are required.

STATEMENT OF NEED

HIV medicine is a rapidly changing discipline characterized by new medications, new approaches to antiretroviral therapy, and ongoing identification of complications and therapeutic approaches to address these complications. These changes are presented in multiple journal articles as well as multiple scientific conferences and frequently assimilated into treatment guidelines. Although this information is theoretically accessible, most practicing physicians may not subscribe to all relevant journals nor do not have time to review the articles, not to mention travel to conferences with limited attendance capabilities. The overall need, addressed by the HIV Report, is keeping abreast of the latest information in HIV medicine to enable clinicians to provide state-of-the-art clinical care to their patients.

RESPONSIBILITY

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

LEARNING OBJECTIVES

At the conclusion of this activity, the participant should be able to:

- Implement new developments and recommendations in antiretroviral therapy, including when to initiate therapy, the use of improved regimens and drug combinations, management of adverse drug effects and drug interactions, therapeutic tactics to deal with viral resistance, and how to deal with complications of therapy
- Discuss the changing epidemiology of opportunistic infections/conditions and HIV comorbidities as well as the current strategies for prevention and treatment.
- Describe new developments in pharmacology associated with HIV infection, including newly approved antiretroviral drugs, new drug targets, drugs in the development pipeline, and the pharmacology of drugs used in the management of HIV infection.

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REFERENCES TO UNLABELED OR UNAPPROVED USES OF DRUGS OR DEVICES

Dr. Gallant - Rilpivirine for first-line therapy (investigational drug); once-daily nevirapine with tenofovir + lamivudine (study regimen).

Dr. Lucas - Raltegravir (investigational drug)

Dr. Gebo and Wilson - Tenofovir, emtricitabine, truvada

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THE HOPKINS HIV REPORT

A bimonthly newsletter for healthcare providers

Report From Los Angeles: The 14th Conference on Retroviruses and Opportunistic Infections (CROI)

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Management of Treatment-Naïve Patients

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

For the first time, the mid-winter CROI meeting was held in a “warm” city—Los Angeles. LA didn’t turn out to be very warm by southern California standards, but at least it wasn’t Boston or Chicago. Most of the big news from CROI pertained to new drugs for treatment-experienced patients, including raltegravir and maraviroc (see *New Data on Treatment-Experienced Patients and Drug Resistance* on p 4). However, some studies were presented that had relevance to initial therapy.

Rilpivirine vs. Efavirenz

Rilpivirine (TMC278), another second generation non-nucleoside reverse transcriptase inhibitor (NNRTI) from Tibotec, has the advantages of a long half-life and high potency at low doses, making it a logical candidate for initial therapy and for eventual coformulation. Study TMC278-C204, presented by Anton Pozniak, was a phase IIB study in which 600 treatment-naïve patients were randomized to receive one of 3 doses (25, 75, or 150 mg daily) of rilpivirine or efavirenz (EFV) plus either zidovudine/lamivudine (AZT/3TC)



Los Angeles Central Library, by Joel Meneses

or tenofovir/emtricitabine (TDF/FTC) [Abstract LB144]. At 48 weeks, there was no difference among arms in the proportion of patients with viral loads below 50 c/mL, with approximately 80% of participants achieving that goal using an intention to treat (ITT), non-completer=failure analysis. Notably, there were more central nervous system (CNS) side effects, rash, and hyperlipidemia in the EFV arm. Since the study was not blinded, the difference in CNS side effects, which are both suggestible

and subjective, may be hard to evaluate. However, the rash and lipid effects are more objective. Rilpivirine could represent the first real threat to the dominance of EFV as the cornerstone of first-line therapy.

Viral Dynamics in ACTG 5142

The results of ACTG 5142 were first presented at the International AIDS Conference in Toronto last year [Riddler S, et al. Abstract THLB0204]. In that study

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the combination of EFV plus 2 nucleoside analog reverse transcriptase inhibitors (NRTIs) was virologically superior to the combination of lopinavir/ritonavir (LPV/r) plus 2 NRTIs. However, there was a significantly greater CD4 response in LPV/r-treated patients, and the resistance consequences of failure with EFV were greater than with LPV/r.

In Los Angeles, we heard a presentation on viral dynamics in this study that may at least partially explain the superior virologic outcome with EFV [Haubrich R, et al.

Abstract 137]. Phase I viral decay was assessed in a substudy of 5142, with viral load measurement at 2, 7, 10, and 14 days. Phase I decay was found to be fastest in EFV-treated patients, and was highly correlated with day 7 viral load reduction, which had been measured in the overall study population. Therefore, the investigators looked further at 7-day viral load decline in all patients. They found that it was significantly greater among EFV-treated subjects, and that a greater 7-day viral load decline was associated with a lower risk of virologic failure at 24, 48, and 96 weeks. Some have argued that the superior response with EFV observed in ACTG 5142 was due to greater tolerability or convenience; however, the current study suggests that differences in potency may have played a role.

Another presentation from 5142 looked at metabolic complications and lipoatrophy [Haubrich R, et al. Abstract 38] and will be discussed in greater detail in the May 2007 issue. Not surprisingly, lipoatrophy occurred most frequently in stavudine (d4T)-treated patients, was intermediate in those taking AZT, and was no different among TDF-treated patients than in those on the NRTI-sparing arm of LPV/r plus EFV. What surprised most of us in the audience was that loss of limb fat, as defined by DEXA, was significantly more common among EFV recipients than among those taking LPV/r, and that the lipid benefits of EFV were confined to triglycerides. This study will probably have little effect on clinical practice, since the move away from thymidine analogs has diminished concerns

about emerging lipoatrophy. Nevertheless, the difference between EFV and LPV/r was unexpected and must be explained. Lipoatrophy is clearly not a direct side effect of EFV, since it was not observed in those taking EFV plus LPV/r without NRTIs. It's also not a simple EFV vs. PI difference, since lipoatrophy was less common with EFV than with nelfinavir in ACTG 384. There is presumably an interaction between EFV and NRTIs that increases the risk of fat loss, but this interaction has not yet been defined.

Once vs. Twice Daily LPV/r: ACTG 5073

Data were presented from ACTG 5073, a study comparing once- vs. twice-daily LPV/r (soft-gel formulation), combined with FTC plus either TDF or extended release d4T [Mildvan D, et al. Abstract 138]. A subset of those randomized to the once-daily arm received directly observed therapy (DOT) for the first 24 weeks. There was no difference in the primary endpoint: time to virologic failure at 48 weeks, either between once and twice daily LPV/r or for self-administered therapy vs. DOT. However, in a subset analysis, patients with baseline viral loads above 100,000 c/mL were more likely to fail with once daily therapy than with twice daily therapy. This is consistent with pharmacokinetic data, which has shown lower and more variable LPV trough concentrations with once daily administration. However, it is not consistent with the Abbott 418 study, in which no difference in efficacy was observed across all viral load strata.

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Management of Treatment-Naïve Patients

Current labeling supports the use of once daily LPV/r for PI-naïve patients, in whom lower LPV trough levels are presumably still high enough to suppress fully susceptible virus. However, the DHHS guidelines list once-daily LPV/r as an alternative regimen. It's worth noting that most of the data on once-daily LPV/r come from studies in which the older soft-gel capsule formulation was used. Once-daily use of the new tablet formulation is easier because of lower pill burden and better tolerability.

DAUFIN: Once vs. Twice Daily Nevirapine

The DAUFIN study compared two regimens in treatment-naïve patients: twice daily AZT/3TC plus nevirapine (NVP) vs. once daily TDF, 3TC, and NVP [Rey D, et al. Abstract 503]. The intention was to enroll 250 subjects, but the study was stopped after enrollment of only 71 participants because of unexpectedly high rates of virologic failure (25%) and resistance, including NNRTI mutations, K65R, and M184V, in the once-daily arm. There was also a high rate of discontinuation in the AZT/3TC arm, mostly due to adverse events. The reason for the failure of the once-daily regimen isn't known. Since there was no arm in which AZT/3TC was combined with once-daily NVP and no arm combining TDF plus 3TC with twice-daily NVP, we can't say whether the failure was due to once-daily administration of NVP, the combination of NVP with TDF and 3TC, or both. However, NVP concentrations were adequate in the once-daily arm, making it unlikely that these findings can be explained

on a purely pharmacokinetic basis. Failure was more common among patients with high baseline viral loads and/or low baseline CD4 counts. This study emphasizes the importance of using well tested regimens, and avoiding regimens that *should* work but that have not been formally studied.

Studies of Didanosine for Initial Therapy

The GESIDA 3903 study compared AZT/3TC plus EFV with didanosine (ddI), 3TC, and EFV in 369 treatment-naïve patients at 45 sites [Berenguer J, et al. Abstract 504]. In a preliminary 24-week analysis, there was no difference in the proportion of patients with viral loads below 50 c/mL by ITT analysis (71% in ddI-treated patients vs. 66% in AZT-treated patients, $p=0.16$). Similarly, there was no difference in virologic response by on-treatment analysis. Patients in the ddI arm had a mean CD4 increase of 128 cells/mm³, compared to 110 in the AZT arm. There was significantly more drop-out due to hematologic toxicity in the AZT arm.

The combination of ddI, EFV, and either 3TC or FTC has not been widely used, but it has demonstrated efficacy in a number of uncontrolled trials or trials in which it was compared against non-standard regimens. In this trial, preliminary results suggest advantages over the standard regimen of AZT/3TC plus EFV. However, AZT has been replaced for first-line therapy by TDF and abacavir (ABC), which are better tolerated and less toxic. Given its potential to cause pancreatitis and neuropathy, it is unlikely that ddI will ever be used for first-line therapy in the developed world. However, generic versions are available, and

there are arguments, both from toxicity and resistance standpoints, supporting its use as an alternative to thymidine analogs in resource-limited settings.

The Tshepo study, conducted in Botswana, randomized 650 treatment-naïve patients to one of six initial regimens [Bussmann H, et al. Abstract 507]. NRTI backbones included AZT/3TC, d4T/3TC, and AZT/ddI. In addition, patients were randomized to receive either EFV or NVP. At two years, an impressive 95.5% of patients taking AZT/3TC or d4T/3TC still had viral loads below 400 c/mL. However, failure with resistance was observed in 11% of those on AZT/ddI compared with only 2% on the two other NRTI backbones ($p=0.002$), and this arm was prematurely terminated based on the recommendation of the Data Safety and Monitoring Board. Common resistance mutations included thymidine analog mutations, especially at codons 67, 70, and 215. Mortality was low in this study, but treatment-modifying toxicity was common, occurring in 18% of participants. Frequent toxicities included anemia, lipodystrophy, severe skin rashes, and lactic acidosis. The Tshepo study also compared DOT with standard of care, and found no significant difference in outcome, presumably because of the high rates of adherence and low rates of virologic failure in the overall study population.

This study demonstrates the fact that HAART can be highly effective and durable in resource-limited settings, but also points

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New Data on Treatment-Experienced Patients and Drug Resistance

By Gregory M. Lucas, M.D. Ph.D.

Sunny Los Angeles afforded a nice respite from the dreary February doldrums of Baltimore, if you were fortunate enough to make it out of the airport before the storm. At this year's CROI, data from new drugs continue to be very encouraging for the treatment of experienced patients.

Raltegravir (MK-0518) in Treatment-Experienced Patients

Raltegravir (RAL) is an HIV integrase inhibitor in phase III clinical trials that is currently available through expanded access. Sixteen-week data from the BENCHMRK-1 and -2 studies were presented in the late-breaker session by Cooper and Steigbigel in paired presentations [Abstracts 105aLB and 105bLB], the combined results of which are summarized below. In these trials, which have identical designs, 699 subjects with HIV RNA >1,000 c/mL and genotypic or phenotypic resistance to ≥ 1 drug from NRTI, NNRTI, and PI classes were randomized 2:1 to RAL plus optimized background (OBR) or placebo plus OBR. The average baseline CD4 count and viral load were 150 cells/mm³ and 40,000 copies/mL, respectively. Between 19% and 21% of subjects used enfuvirtide (ENF) for the first time as part of the OBR and 25%-50% used darunavir (DRV) for the first time. Thirty percent of participants had no active drugs in the OBR. At 16 weeks, HIV RNA <50 c/mL was achieved by 61% to 62% in the RAL arms compared to 33% to 36% in the placebo arms ($p < 0.001$ for all comparisons with placebo). The average increases in CD4 cell counts were 83 to 86 cells/mm³ in the RAL arms compared to just

31 to 40 cells/mm³ in the placebo arms ($P < 0.001$). RAL showed clear evidence of efficacy in all subgroups analyzed and adverse events were similar in the RAL and placebo arms. Genotypic changes were identified in the HIV integrase gene in 32 of 41 individuals with available samples who experienced virologic failure in the RAL arm.

CCR5 Inhibitor, Maraviroc, in Treatment-Experienced Patients

The efficacy of maraviroc (MVC) is being evaluated in treatment-experienced patients with R5-tropic virus in the MOTIVATE-1 and -2, phase III trials. It is noteworthy that only about 50% of highly treatment-experienced patients have R5-tropic virus, and MVC is not effective against X4-tropic or dual/mixed-tropic virus. Twenty-four-week results from the MOTIVATE trials were presented at the late-breaker session by Lalezari and Nelson in paired abstracts [Abstracts 104aLB and 104bLB], combined results from which are presented here. Triple-class-experienced/resistant subjects ($n = 1,076$) with viral load >5,000 c/mL and R5-tropic virus were randomized 1:2:2 to 1 of 3 arms, OBR plus placebo or OBR plus MVC (dosed once or twice daily). Patients receiving a PI (other than tipranavir) or delavirdine received 150 mg of MVC; all others received 300 mg of MVC (in each case MVC was dosed once or twice daily according to study arm allocation). The average CD4 cell counts and viral load levels were 170 cells/mm³ and 4.9 log₁₀ c/mL, respectively, and two-thirds of patients had fewer than 2 active drugs in their OBR. At

24 weeks the percent of participants with viral load <50 c/mL was 21% to 25% in the placebo arms, compared to 41% to 46% in the MVC arms (all comparisons with placebo statistically significant). Suppression rates were similar whether MVC was dosed once or twice daily. The average CD4 cell increases from baseline were 52-64 cells/mm³ in the placebo arms versus 102-111 cells/mm³ in the MVC arms.

10% of Treatment-Naïve Patients Have Drug-Resistant HIV, Maybe More if We Look Harder

Wheeler and colleagues presented data from the CDC Variant, Atypical, and Resistance HIV Surveillance System (VARHS) [Abstract 648]. Samples from 3,130 newly diagnosed HIV-infected subjects who were identified from 11 study sites in the US between 2003 and 2006 were tested for major drug resistance mutations. Overall, 10.4% of participants had drug resistance detected, with resistance to NNRTIs (6.9%) being more frequent than NRTI (3.6%) or PI (2.4%) resistance. Individuals with virus harboring resistance mutations to 2 or 3 drug classes were rare, 1.4% and 0.5%, respectively. This latest report is in line with prior data, which have estimated that between 5% and 15% of untreated individuals have drug resistance virus (<http://www.aidsinfo.nih.gov>).

A key limitation of standard resistance tests is that viral variants that represent <20% of the total population are not detected. However, a sensitive real-time polymerase chain reaction (PCR) can detect mutations at frequencies below 1%. The



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disadvantage of this technique is that specific mutations must be sought, rather than sequencing the entire region of interest for all mutations. Use of real-time PCR garnered attention two years ago when it was reported that at least 65% HIV-infected women who received single-dose nevirapine (sdNVP) to prevent mother to child transmission had evidence of NNRTI mutations using the sensitive method, compared to an estimated 30% to 40% using standard genotyping methods [Johnson JA, et al., *J Infect Disease* 2005;192:16].

At this year's CROI, Johnson and coworkers presented results from a study that used same rationale and methods to look for hidden resistance in treatment-naïve subjects [Abstract 639]. The researchers used real-time PCR on HIV RNA samples from 507 newly diagnosed, treatment-naïve individuals to search for the following mutations: reverse transcriptase – M41L, K70R, K103N, Y181C, M184V, T215F, T215Y; protease – L90M. Among 205 subjects who had wild-type virus by standard genotype, 30 subjects (15%) had at least one of the above mutations detected by the real-time PCR method – most frequently the K70R, M41L, or K103N. Moreover, among 302 subjects with at least one drug mutation identified by standard genotype, 7% had resistance detected to another drug class by the real-time PCR method. Similarly, Paredes and colleagues found that real-time PCR identified more HIV-infected, treatment-naïve pregnant women who harbored the M184V mutation in reverse transcriptase or the

D30N mutation in protease than did standard genotyping [Abstract 658].

A burning question that arises from these data is whether mutations detected by ultrasensitive techniques are clinically relevant to the treatment of naïve patients. Johnson and colleagues [Abstract 639] took preliminary steps to address this issue by using real-time PCR to look for K103N, Y181C, and M184V in baseline samples from 316 treatment-naïve subjects who were starting treatment with efavirenz (EFV) plus lamivudine (3TC) plus abacavir (ABC) or zidovudine (AZT) in one of three clinical trials. Seven subjects had resistance mutations identified by standard bulk sequencing and 9 additional participants with resistance mutations were identified by real-time PCR. Seven of these 9 (78%) experienced virologic failure at 48 weeks, at rate that was significantly higher than the overall failure rate in the clinical trials of 30% ($P=0.004$).

Phenotypic Clinical Cutoffs Calculated for Darunavir (DRV)

Coakley and colleagues determined upper and lower fold-change cutoffs for phenotypic susceptibility to DRV using data from participants in the POWER studies [Abstract 610]. Subjects who used ENF were excluded from the analysis and the predicted activity of other drugs in OBR was adjusted for. Virologic changes from baseline to weeks 2, 4, and 8 were considered in formulating cutoffs. The lower clinical cutoff was defined as the fold-change in phenotypic susceptibility at which less than maximal virologic response to DRV was observed. The upper cutoff was

defined as the fold-change in phenotypic susceptibility at which HIV RNA decreases from baseline were $<0.3 \log_{10} \text{ c/mL}$ (e.g., no meaningful response). The lower and upper clinical cutoffs for DRV were determined to be 10-fold and 90-fold changes in phenotypic susceptibility, respectively. At 6 weeks, the change in viral load from baseline in participants in the susceptible category ($\text{FC}<10$, $n=96$) was $-2.3 \log_{10} \text{ c/mL}$, compared to $-1.3 \log_{10} \text{ c/mL}$ in the intermediate category ($10<\text{FC}<90$, $n=71$), and $-0.4 \log_{10} \text{ c/mL}$ in the resistant category ($\text{FC}>90$, $n=5$).

PI Sequencing: Darunavir Before Amprenavir, Need to Fear; Amprenavir before Darunavir, in the Clear

Concern has been raised that prior exposure to amprenavir (APV, now formulated as fosamprenavir) may compromise the subsequent activity of DRV more so than resistance to other PIs. APV and DRV are structurally related, and APV shares 6 of the 11 protease mutations that have been linked to reduced susceptibility to DRV (V32I, I47V, I50V, I54L/M, G73S, I84V). Data presented in Los Angeles provided reassurance that prior use of APV is not an Achilles heel for DRV. Parkin and colleagues assessed samples from a clinical database for cross-resistance patterns between DRV and other PIs [Abstract 607]. Although the correlation coefficient for IC_{50} fold-change was highest for APV and DRV, indicating an association, there was little to indicate that APV resistance translated into a high risk of DRV resistance. For example,

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only 12% of 1,340 samples that showed high-level resistance to APV demonstrated high-level resistant to DRV (fold-change >90), and 39% of these samples were fully susceptible to DRV (fold-change <10). This level of clinical cross-resistance was quite similar in comparisons between tipranavir (TPV) or lopinavir (LPV/r) and DRV. The converse, however, was not true. Among 855 isolates that demonstrated high or intermediate resistance to DRV (fold-change >10), 854 (99.9%) had high-level resistance to APV, compared to 734 (86%) to LPV/r and 416 (49%) to TPV.

Picchio and colleagues further explored the concern of APV/DRV cross-resistance in a retrospective analysis of data from the POWER studies, in which OBR plus DRV/r or placebo was compared in highly treatment-experienced patients [Abstract 609]. This group reported that prior APV use or resistance did not appear to have a large effect on the 48-week response to DRV. As shown in the table, 48-week

Table. Response to DRV/r in the POWER Studies Overall and in Subgroups Defined by Prior Exposure and Resistance to LPV or APV

Patient Group	Week 48 Results	
	Mean HIV RNA Change (log ₁₀ c/mL)	HIV RNA < 50 c/mL, %
All subjects	-1.65	45
Failed LPV and had predicted fold-change to LPR above upper clinical cutoff	-1.48	42
Failed APV (or FPV) and had predicted fold-change to APV above upper clinical cutoff	-1.43	36

outcomes with DRV/r were similar for participants with baseline exposure or resistance to APV and LPV.

Summary

The first integrase inhibitor likely to receive FDA-approval has demonstrated impressive efficacy at 16-weeks in the BENCHMRK studies. Phase II data presented by Markowitz at last year's International AIDS Conference [Abstract THLB0214] intimate that this drug may

even be able to give efavirenz a run for first-line therapy. Maraviroc also has demonstrated impressive early efficacy in experienced patients in the MOTIVATE trials. CCR5 inhibitors like maraviroc, however, have an inherent limitation in treatment experienced patients, in that up to 50% of such individuals cannot benefit from these agents because of the presence of X4-tropic or dual/mixed-tropic virus. In contrast, R5-tropic virus is nearly universal in acute HIV infection and is also found in a high percentage in chronically infected, treatment-naïve individuals. The most recent data from the CDC indicate that drug resistance in newly-diagnosed individuals remains stable at approximately 10%. However, more sensitive detection methods have suggested that we might just be seeing the tip of the iceberg with standard population genotypic assays. More data correlating real-time PCR results with clinical outcomes are needed. Finally, data presented at the conference provided reassurance that use of FPV is not likely to affect response rates to DRV. ▲

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The 14th CROI demonstrated the increasing importance of viral hepatitis in the management of chronic HIV infection. There were numerous abstracts presented as posters and two oral sessions devoted to the management of viral hepatitis. Some of the most interesting findings of the meeting were the discussion of the utility of liver biopsy and other markers in the staging and management of hepatic disease, appropriate vaccination of patients against hepatitis B virus (HBV), the low treatment rates of hepatitis C virus (HCV) infection among injection drug users (IDUs), and the potential dangers of using entecavir in patients co-infected with HIV and HBV who are not on HAART.

Alternative Markers for Fibrosis

David Thomas commented on assessment of liver fibrosis among those chronically infected with HIV and HCV [Abstract 161]. He postulated that the gold standard, the liver biopsy, is inherently limited in accuracy due to sampling error, heterogeneity of the diseased liver, and inter- and intra-observer variability among pathologists. However, other noninvasive markers of liver fibrosis, including transient hepatic elastography and serum markers of inflammation and collagen deposition are also limited. Given the inherent inaccuracy of the liver biopsy, it is difficult to accurately predict the true sensitivity and specificity of the noninvasive markers. Thomas proposed that, given current data, it may be safer and as informative to use an optimal panel of noninvasive markers to evaluate liver fibrosis, especially if HCV/HIV co-infected patients are followed longitudinally and the tests repeated serially.

There were 10 posters addressing the noninvasive assessment of liver damage among patients co-infected with HIV and either hepatitis B or C [Abstracts 908-917]. Many abstracts compared various predictive models of liver fibrosis and disease using serum markers. Abstracts 912 through 914 compared multiple markers and validated specific markers, such as FIB-4, FORNS, APRI, or hyaluronic acid, as good predictors of severe fibrosis, but inaccurate as markers of more moderate disease that would indicate clinically significant fibrosis still requiring initiation of HCV or HBV treatment. Suzman and colleagues generated a predictive model of fibrosis among HCV-infected patients using various serum markers. The investigators found that $\alpha 2$ macroglobulin and haptoglobin combined with 2 genes (alanyl amino peptidase and mitogen activated protein) to be most predictive of Ishak fibrosis score F3 or above (area under receiver operator curve, or AUROC, 0.92) in HIV/HCV co-infected patients [Abstract 908]. Cacoub and colleagues evaluated non-invasive liver fibrosis biomarkers in 274 treatment-naïve French patients and found that the various markers (Fibrometer, Hepascore and Fibrotest) can only correctly classify patients with severe fibrosis (\geq F3, accuracy 74 to 97%) [Abstract 909]. They found Fibrometer to be most accurate for F2 or F3 and above, while Fibrotest was most accurate for F1 or less. Nunes and colleagues evaluated numerous noninvasive markers for predicting end-stage liver disease (ESLD) events in HCV-infected patients [Abstract 916]. In this study, the

best marker was hyaluronic acid with AUROC of 0.92 and APRI score, with an AUROC of 0.90.

Two abstracts assessed transient hepatic elastography, a measurement of liver stiffness. Vergara and coworkers used Fibroscan to distinguish clinically significant fibrosis in HCV/HIV co-infected persons [Abstract 910]. Liver biopsies were paired with elastography among HCV-untreated subjects. Using the standard Fibroscan cut-off of 7.2 kPa, 19% of those with METAVIR fibrosis scores (a score based on basic pathological features) greater than F1 were misclassified. The AUROC for Fibroscan >7.2 KPa for F4 was 0.95, for F3 0.93 and for F2 0.87, all considered good predictors. Mialhes and colleagues assessed those on treatment for both HBV and HIV infection, with Fibroscan versus liver biopsy for concordance [Abstract 911]. AUROC for METAVIR F0-F2 vs. F3-F4 was 0.73 and for F0-F1 vs. F2-F4 was 0.79. Duration of therapy and suppression of HBV were not reported.

Two other abstracts looked at novel predictors of fibrosis due to HCV infection. Shuart established that soluble TNF receptor II levels may be increased as a result of HIV infection, and this elevation may accelerate liver fibrosis [Abstract 915]. Salmon and colleagues demonstrated that insulin resistance among those with HCV/HIV co-infection independently predicts liver fibrosis, although this abstract did not indicate which patients were on

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antiretroviral therapy [Abstract 917]. A group from England suggested that steatosis in HCV/HIV co-infected patients is independently associated with advanced liver fibrosis [Mohsen A, et al., Abstract 926]. Finally, several groups showed that progression from fibrosis to cirrhosis or death is faster among those infected with HIV and HCV (plus or minus HBV) than in those with HIV and HBV, perhaps because of HBV suppression with antiretrovirals such as tenofovir (TDF), lamivudine (3TC), and/or emtricitabine (FTC) [Abstracts 931-933].

Vaccinations

HIV-infected patients are less likely to respond to HBV vaccination than the general population. Several groups evaluated different regimens for HBV vaccination to achieve higher rates of seroconversion. Vries-Sluijs and colleagues revaccinated all patients who did not seroconvert after one HBV series with high dose recombinant vaccination at monthly intervals (0, 1, 2 months) [Abstract 883]. Of 144 patients revaccinated, 51% demonstrated a response. Responders were more likely to be female and younger than non-responders. In a similar abstract from Ireland, Low found that double-dosing patients increased response rates in non-responders; 87% of non-responders seroconverted after the double dosing regimen [Abstract 884]. Of note, all of those with CD4 counts >500 cells/mm³ seroconverted, suggesting that vaccinating before the CD4 count falls below 500 or waiting until HAART has boosted the CD4 count may improve response rates.

Treatment

Sulkowski and colleagues evaluated treatment rates among treatment eligible IDUs with and without HIV infection followed in the Johns Hopkins Moore clinic [Abstract 947]. He found that while 80% of HCV mono-infected patients were eligible for treatment, only 50% of HIV-HCV co-infected patients were eligible for HCV treatment. The most common reasons for exclusion were severe depression, life expectancy less than 2 years, and hematologic abnormalities. Even after the removal of financial and geographic barriers, only 40% of eligible IDUs obtained HCV treatment, suggesting that better strategies for engaging and retaining HCV infected IDUs in care are essential.

Standard management with pegylated interferon/ribavirin (PEG-IFN/RBV) in the HCV/HIV co-infected patient involves monitoring HCV RNA response at week 12 of therapy to determine the rapid virological response (RVR); this helps determine the utility of continuing therapy for the full 24 or 48 weeks. Two abstracts assessed whether evaluation of HCV RNA response at 4 weeks (early RVR) was equally predictive of sustained virological response (SVR) as the traditional 12 week evaluation. Mira and coinvestigators evaluated 101 HCV/HIV co-infected patients treated with PEG-IFN/RBV [Abstract 891]. Ninety seven percent of patients with RVR (undetectable HCV RNA) had SVR, for a positive predictive value (PPV) of 97%. Those with HCV genotype 3 treated for 24 weeks had a PPV=100% for SVR with early RVR checked at 4 weeks. The highest negative

predictive value (NPV=96%) was found when the HCV RNA failed to decrease by more than 0.6 log₁₀ at 4 weeks, where failure of SVR could have been predicted in 24% of patients and treatment thus discontinued at 4 weeks. The authors point out that the use of these 2 cutoffs could predict the SVR after 4 weeks in 60% of HIV/HCV co-infected patients on HCV therapy. Likewise, O'Shea and colleagues evaluated early RVR at week 4 in 55 HCV/HIV coinfecting and 77 HCV mono-infected patients undergoing HCV treatment [Abstract 894]. Sixty-seven percent of HCV/HIV co-infected patients achieved early RVR (HCV RNA decline >2 log₁₀ or undetectable), with a PPV of 92% and NPV of 88%. Similar predictive values were seen for HCV mono-infected patients as well. Separate analyses by HCV genotype were not reported. These data could have substantial clinical utility, as those with early RVR at 4 weeks would have strong motivation to continue therapy, while those without early RVR would be less likely to respond, and could avoid treatment-related side effects and costly therapy.

Treatment of Hepatitis B Co-Infection

Chloe Thio provided a comprehensive overview of the management of hepatitis B infection [Abstract 48]. She summarized some of the most important treatment developments over the past 5 years, including the appropriate treatment of HBV/HIV co-infected patients who need HAART (TDF plus either FTC), who do not need HAART (IFN, adefovir dipivoxil, or telbivudine), and who are 3TC-experienced, indicating that they probably have 3TC resistance (add tenofovir). She



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explained the limitations for each of the available options for treating patients who do not have an indication for starting HAART. She also cautioned against cross-resistance that can develop between lamivudine, telbivudine, and entecavir, but less commonly between these drugs and adefovir/tenofovir. In addition, she presented a patient with HBV/HIV co-infection treated with entecavir for HBV who did not have documented M184V mutation prior to entecavir treatment [Abstract 136LB], although he had previously received a lamivudine-containing antiretroviral regimen. Despite previous data suggesting that entecavir has no inherent anti-HIV activity, the patient developed a 1 log drop in HIV RNA after initiation of treatment, and the M184V mutation emerged suggesting that entecavir does have antiretroviral activity against HIV and that it can select for M184V. The implications of this study are that patients co-infected with HBV and HIV should not be treated with entecavir monotherapy without careful consideration of other options, and that treatment for both infections should be considered whenever possible.

Findings presented at the 14th CROI demonstrated that viral hepatitis is an increasing cause of morbidity and mortality, that successful vaccination of HIV infected patients may require additional vaccines beyond the traditional 3 shot series, questioned the accuracy of liver biopsy and suggested that alternative non-invasive measures of liver fibrosis may be beneficial in the management and treatment of hepatitis co-infection in HIV infected patients. ▲



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CD4 Lymphocyte Depletion: Where Have All The Cells Gone?

By Scott Kim, M.D. and Joel N Blankson, M.D., Ph.D.

It has been 21 years since HIV was first isolated and demonstrated to be the cause of AIDS. Progressive CD4 cell depletion has been identified as the fundamental basis of AIDS, but the specific mechanism by which this cell death occurs is still not well understood. It is well accepted that in chronic disease less than 1% of all CD4 cells are infected. The proportional loss of CD4 cells in AIDS far exceeds this prevalence of cell infection, implying that a direct cytopathic effect of the virus cannot be the sole explanation of CD4 cell depletion. In recent years it has been shown that during acute infection there is massive depletion of CD4 cells in the gastrointestinal associated lymphoid tissue (GALT) and other mucosal tissues. Importantly, CD4 cell depletion in these tissues appears to be significantly greater than that observed in peripheral blood.

This important topic stimulated intense discussion at last year's CROI. In particular, many investigators wondered why this dramatic depletion of GALT CD4 cells was not accompanied by clinical symptoms such as an increase in the incidence of enteric infections. This topic continued to receive a lot of attention this year and data were presented suggesting that depletion of CD4 cells in the gut could in fact have clinical consequences.

Brenchley and colleagues expanded on their prior work on GALT depletion by elaborating a pathophysiologic model by which gut-associated CD4 cell loss in primary infection may be directly responsible for the progressive CD4 cell loss that leads to AIDS [Abstract 65]. They documented high levels of lipopolysaccharide LPS, a component of bacteria cell walls, in the plasma of untreated HIV-infected patients. The levels of LPS in these patients

were significantly higher than the levels found in patients on HAART and in HIV-negative patients. The investigators suggested that these high levels of LPS are due to microbial translocation that results from the initial loss of gut-associated lymphocytes. They proposed that this microbial translocation leads to systemic immune activation, as the immune system responds to the potential pathogens crossing the enteric barrier. Activated CD4 lymphocytes recruited to the gut are predisposed to HIV infection and thus affected by direct viral cytotoxicity, preventing any durable repletion of GALT. Systemic immune activation also leads to long-term depletion of CD4 cells in other compartments, by means of deleterious changes in cell homeostasis and life cycle. This cycle of microbial translocation, immune activation, and death of activated lymphocytes contributes to the chronic CD4 cell loss that leads to AIDS.

While this provocative model has received a lot of attention, it is based almost entirely on the elevated LPS levels found in untreated chronically infected patients. Prior studies have demonstrated that LPS may be significantly elevated in disease states like diabetes, in which neither GALT depletion nor significant enteropathy occurs [Creely, et al. *Am J Physiol Endocrinol Metab* 2007;297:E740-7]. Furthermore no direct evidence linking microbial translocation to immune activation was presented. Clearly a lot more work needs to be done in this area.

A separate issue that also received significant attention was the reversibility of HIV-related GALT depletion. Prior investigations had suggested that CD4 cell depletion in gut mucosal tissue occurred within the first several weeks of HIV infection and



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that significant GALT repletion thereafter was rare, possibly associated with localized control of HIV replication, and unrelated to timing of HAART initiation [Guadalupe M, et al. *J Virology* 2006; 80:8236-47]. Shenefelt and others presented countervailing data at CROI 2007 to suggest that significant CD4 cell repletion in GALT, in fact, does occur in response to HAART [Abstract 28]. The investigators argued that prior studies had underestimated the CD4 cell population by relying on estimations based on flow cytometry; in this study, they followed absolute cell counts from colonic biopsies in a cohort of 8 patients who started HAART. By cellular staining of tissue sections and immunofluorescent microscopy, they estimated that by 24 weeks of HAART, the GALT CD4 cell population had been reconstituted to 52% of normal levels, while peripheral blood CD4 cells had only increased to 19% of normal levels. Additionally, they reported evidence of lymphoid aggregate reconstitution as well, which had not previously been observed. Further reconstitution between 24-48 weeks after HAART initiation was not observed, suggesting that the benefit of HAART was largely achieved in the first 24 weeks of treatment. A shortcoming of the study was the lack of flow cytometry experiments, which would have provided a basis for comparison between their data and seemingly opposing data from prior investigations.

Other investigators have turned to animal models to more closely investigate the mechanisms involved in CD4 cell depletion. Mario Roederer and colleagues inoculated rhesus macaques with SIV and showed that memory CD4 cells are infected to a much higher extent than naïve CD4 cells [Abstract 95]. By 14 days after infection, approximately 80%

of these cells are deleted in the GALT and other mucosal tissue, and PCR analysis suggests that direct infection can explain this massive CD4 depletion. Thus, in contrast to chronic infection, where the cytopathic effect of infection alone cannot explain the progressive CD4 loss, it appears that in primary infection, the majority of CD4 cells die as a direct consequence of infection. In this model the degree of CD4 cell depletion in primary infection was highly correlated with progression to death. Interestingly, a vaccine that markedly reduced viral replication in primary infection also reduced the number of cells that were lost.

In a plenary session, Louis Picker gave a detailed total body analysis of CD4 cell depletion after SIV infection of rhesus macaques [Abstract 14]. Radioisotope labeling demonstrated a high turnover of both CD4 and CD8 cells in infected monkeys. Since CD8 cells are not infected, it is likely that immune activation is the cause of the high turnover of both cell types in chronic infection. He described two distinct types of memory CD4 cells, central memory cells that are capable of proliferative renewal and effector memory CD4 cells that are more differentiated and less capable of proliferation. The effector memory cells are infected very efficiently, but homeostasis is maintained through proliferation of central memory cells, which differentiate into effector memory cells. The infection rate of central memory CD4 is low, but eventual depletion of these cells occurs, leading to insufficient effector memory cell production and AIDS. Picker proposed that AIDS may be best considered as a disease that results

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out that drug toxicity is common, an important concern in countries with few options for treatment modification. It also emphasizes the point made by so many other studies: that NRTI-containing initial regimens should include either 3TC or FTC.

Observational Studies Supporting Efavirenz for First-Line Therapy

An analysis of the Veterans Administration database looked at choice of first-line antiretroviral regimen in over 6000 patients [Braithwaite S, et al. Abstract 520]. Overall adherence was poor in this predominately black, male veteran population, with only 63% of prescriptions being filled as prescribed. However, adherence was better among EFV-treated patients, and those on EFV were more likely to have undetectable viral loads after 1 year. The virologic superiority of EFV was less apparent when it was compared against newer ritonavir-boosted PIs (LPV/r and ritonavir-boosted atazanavir or fosamprenavir). In the ART

Cohort Collaborative, an analysis of over 20,000 patients in 16 cohorts found that 6-month viremia was lower with EFV than with all other third agents (combined with AZT/3TC), although this did not translate into a significant difference in clinical outcomes [Mugavero M, et al. Abstract 527].

These cohort studies support the results of ACTG 5142 and other studies that have demonstrated the superiority of EFV-based regimens. However, there is a strong potential for selection bias in observational cohort studies. EFV has often been viewed, perhaps for good reason, as the preferred agent, but one that should be given only to patients most likely to be adherent. As a result of this “cherry picking,” EFV may do better in cohort studies because it’s given to those who would have done well on any regimen. Were patients treated with EFV in the VA study more likely to fill their prescriptions because they were taking EFV, or were they prescribed EFV because they

were more likely to fill their prescriptions? It’s impossible to tease these issues out in these cohort studies, though both factors could have played a role in the ultimate outcome.

Conclusions

From a treatment standpoint, the 2007 CROI will be remembered primarily for the BENCHMRK and MOTIVATE trials (see *New Data on Treatment-Experienced Patients and Drug Resistance* on p 4), which foretell the dawn of a new era in which most HIV-infected patients who are adherent to therapy will be able to achieve virologic suppression despite extensive resistance. The data on initial therapy was less earth-shattering, but still important.

The next important conference will be the International AIDS Society conference, to be held in Sydney in July. Next year’s CROI will be back in chilly Boston, February 3-7, 2008. ▲

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from a failure of central memory CD4 cell homeostasis.

CD4 cell depletion is a fascinating topic that clearly needs further exploration. The results of the studies presented have major implications for the decision of when to initiate HAART. In macaques, the degree of CD4 depletion in primary infection correlates with mortality. If this is also true for HIV infection, then it may make sense to initiate HAART

during primary infection to preserve these cells where possible. However, if treatment with HAART during chronic infection can in fact lead to the replenishment of CD4 cells in mucosal tissue, then treatment during primary infection may not be beneficial. It will also be very important to confirm the hypothesis that CD4 depletion leads to microbial translocation, as this may be another reason to start therapy early. ▲