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AIDS CLINICAL CARE

Genital Shedding of HIV — The Effects of Antiretroviral Therapy and the Menstrual Cycle

Cervicovaginal HIV RNA and proviral DNA were largely undetectable in women on atazanavir-based antiretroviral therapy.

Distribution of antiretroviral drugs into various compartments, including the female genital tract, is not well characterized. Concern has been raised about the possibility of intermittent viral shedding, particularly in the presence of factors known to increase it (sexually transmitted infections, bacterial vaginosis, local inflammation, and menstrual-cycle phase).

To address these concerns, investigators studied 20 HIV-infected women with normal menstrual cycles who were taking TDF/emtricitabine/ritonavir-boosted atazanavir and had documented undetectable plasma HIV RNA. Blood and cervicovaginal (CV) samples were collected twice weekly for 3 weeks and tested for antiretroviral-drug concentrations, HIV RNA, and proviral DNA. If a study visit coincided with menses, sample collection was delayed until after the end of menstruation.

Despite considerable within- and between-person variability, concentrations of all three antiretroviral drugs were higher in CV samples than in concomitant plasma specimens, with CV/plasma ratios of 11.9 for emtricitabine, 3.52 for TDF, and 2.39 for atazanavir. HIV RNA was detected at low levels (<50 copies/mL) in CV samples of 9 women (45%; 16% of all sampling events), and proviral DNA was found in CV samples of 14 (70%; 36% of sampling events). Detection of HIV RNA or proviral DNA in CV samples was not associated with genital antiretroviral-drug concentrations, menstrual-cycle phase, bacterial vaginosis, genital bleeding, or detection of HIV in plasma but was associated with CV inflammation (as evidenced by higher levels of CV leukocytes).

COMMENT

These results provide pharmacological support for the findings of the HPTN 052 study, which suggested that standard dosing of antiretrovirals diminishes HIV transmission. The conclusions must be considered cautiously, given the relatively small sample size and the fact that only two symptomatic vaginal infections were diagnosed during the study. Nonetheless, the data strongly support the benefits of suppressive antiretroviral therapy in reducing sexual transmission of HIV, even in the presence of other factors associated with increased HIV shedding.

— Charles B. Hicks, MD

Note to readers: At the time NEJM Journal Watch reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

Sheth AN et al. HIV-1 genital shedding is suppressed in the setting of high genital antiretroviral drug concentrations throughout the menstrual cycle. **J Infect Dis** *2014 Mar 18; [e-pub ahead of print]. (http://dx.doi.org/10.1093/infdis/jiu166)*

FLAMINGO: Dolutegravir vs. Darunavir for Initial Treatment of HIV

In a randomized trial comparing dolutegravir with ritonavir-boosted darunavir, a higher proportion of patients in the dolutegravir group achieved viral suppression.

In previous phase III trials conducted among treatment-naive HIV-infected patients, dolutegravir-based therapy was found to be noninferior to raltegravir-containing combinations (*NEJM JW AIDS Clin Care* Mar 2013, p. 22, and *Lancet* 2013; 381:735) and superior to an efavirenz-based regimen (*NEJM JW AIDS Clin Care* Jan 2014, p. 3, and *N Engl J Med* 2013; 369:1807). Now, in an open-label, manufacturer-sponsored, phase IIIb study called FLAMINGO, dolutegravir has been compared with a first-line protease inhibitor, ritonavir-boosted darunavir.

Treatment-naive HIV-infected patients were randomized to receive either dolutegravir or boosted darunavir, each combined with investigator-selected nucleoside reverse transcriptase inhibitors (67% received tenofovir/FTC, 33% abacavir/3TC). Most of the 484 patients included in the analysis were male (85%);

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the median baseline CD4 count was ~400 cells/mm^3.

At week 48, 90% of those in the dolutegravir group and 83% of those in the boosted-darunavir group had viral loads <50 copies/mL. In a prespecified secondary analysis, dolutegravir was found to be superior to boosted darunavir, largely because of fewer drug discontinuations, as well as a higher virologic response rate in those with pretreatment viral loads >100,000 copies/mL (93% vs. 70%, by FDA Snapshot analysis). Only two patients in each treatment arm had confirmed virologic failure; no treatment-emergent resistance mutations were detected. Serum creatinine increased more in the dolutegravir group than in the boosted-darunavir group, but the increase was small, and no patient discontinued the study because of renal events. This effect was attributed to a dolutegravir-induced decrease in the tubular secretion of creatinine.

COMMENT

FLAMINGO is the third phase III trial in treatment-naive patients in which dolutegravir has compared favorably with other first-line antiretroviral agents. The absence of treatment-emergent resistance suggests that dolutegravir, like protease inhibitors, has a high genetic barrier to resistance, which makes it attractive in patients who have poor or uncertain adherence; we have much more experience, however, with PIs in this particular population. Long-term monitoring of side effects and efficacy is needed, but clearly the drug is an excellent option for many patients, particularly because it has few drug interactions and no food requirements. With approval anticipated this year of a single-pill dolutegravir/abacavir/3TC combination, use of this regimen is certain to increase. As editorialists observe, however, with more generic antiretrovirals becoming available, weighing the advantages of newer drugs, such as dolutegravir, against their higher costs will be a hot topic for debate.

— Rajesh T. Gandhi, MD

NEJM GROUP
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Clotet B et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. **Lancet** *2014 Apr 1; [e-pub ahead of print]. (http://dx.doi.org/10.1016/S0140-6736(14)60084-2)*

Pozniak AL and Arribas JR. FLAMINGO: How much rosier can antiretroviral therapy get? **Lancet** *2014 Apr 1; [e-pub ahead of print]. (http://dx.doi.org/10.1016/S0140-6736(14)60447-5)*

Early ART Improves Clinical Outcomes: More Results from HPTN 052

Patients who were randomized to initiate antiretroviral therapy early had fewer new-onset AIDS events — especially tuberculosis — than those assigned to delayed therapy.

In the landmark HPTN 052 study, 1763 HIV-serodiscordant couples primarily in Africa, Brazil, Thailand, and India were randomly assigned to early or delayed antiretroviral therapy (ART). The main finding — that early ART reduced HIV transmission by 96% — was a milestone in HIV prevention trials (*NEJM JW AIDS Clin Care* Sep 2011, p. 73, and *New Engl J Med* 2011; 365:493). Now, investigators have examined clinical outcomes in the study participants.

ART was started when the CD4 count was 350 to 550 cells/mm^3 (early group) or when either the CD4 count fell to ≤250 cells/mm^3 or an AIDS-defining illness developed (deferred group). Primary events included death, WHO stage 4 HIV disease, tuberculosis (TB), and serious non-AIDS events (e.g., cardiovascular disease, malignancy). Secondary outcomes included WHO stage 2 and 3 HIV events, malaria, lipodystrophy, dyslipidemia, and other medical disorders associated with HIV or its treatment.

At ART initiation, median CD4 counts were 442 cells/mm^3 in the early ART group and 230 cells/mm^3 in the deferred group. Primary clinical events occurred in 57 and 77 patients, respectively (hazard ratio, 0.73; P=0.074). Early ART was associated with a significant reduction in the 2-year cumulative probability of new-onset AIDS events (3.3% vs. 6.0%; HR, 0.64; P=0.031), particularly TB (1.2% vs. 3.7%; HR, 0.49; P=0.018). The combined incidence of primary and secondary outcomes was 24.9/100 person-years in the early ART group and 29.2/100 person-years in the

deferred ART group (P=0.025). Rates of serious non-AIDS events and overall mortality were similar between groups.

COMMENT

These findings demonstrate a lower probability of AIDS clinical events in HIV-infected patients in low- and middle-income countries who initiate antiretroviral therapy at CD4 counts ≥350 cells/mm^3, compared with ≤250 cells/mm^3. ART's effect on preventing TB was striking, reflecting the trial locations in TB-endemic areas. Observational studies suggest that early ART is also beneficial in high-income countries with low TB rates, such as the U.S. Whether the START study (a randomized trial in 35 countries, including the U.S.) will show improved outcomes with even earlier therapy is uncertain, because event rates are likely to be low. Nevertheless, given the manifest benefits of ART — for both the individual's and the public's health — I think early therapy should be here to stay. ***— Rajesh T. Gandhi, MD***

Grinsztejn B et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: Results from the phase 3 HPTN 052 randomised controlled trial. **Lancet Infect Dis** *2014 Apr; 14:281.*

ART Pill Burden and Dosing Frequency: Do They Matter?

As antiretroviral regimens become more potent and better tolerated, virologic outcomes have improved; regimen simplification has also helped by decreasing pill burden and increasing adherence.

The success of antiretroviral therapy (ART) is directly correlated with adherence, which in turn depends on the convenience and tolerability of the regimens involved. In recent years, ART regimens have become simpler, with lower pill burdens and once-daily dosing.

To evaluate the effects of these changes on ART adherence and virologic suppression, investigators conducted a meta-analysis of relevant randomized, controlled trials published in the literature or presented at conferences in abstract form. Nineteen studies (totaling 6321 adult patients) published between 2004 and 2011 met the inclusion criteria: 11 (totaling 3092 patients) that had been published in a previous meta-analysis (*NEJM JW AIDS Clin Care* Apr 2009, p. 37, and *Clin Infect Dis* 2009; 48:484) plus 8 additional ones (3283 patients). Of these 19 studies, 7 involved treatment-naive patients, 9 evaluated treatment-experienced patients with virologic suppression, and 3 evaluated treatment-experienced patients with virologic failure; the median duration of follow-up was 48 weeks. Seventeen of the studies reported both adherence and virologic suppression.

Higher pill burden was significantly associated with lower adherence for twice-daily regimens and with worse virologic outcomes for both once- and twice-daily regimens. Adherence rates were modestly higher with once-daily than with twice-daily regimens, but virologic-suppression rates showed no significant difference. Adherence and virologic-suppression rates both decreased over time; however, the decrease in adherence was less with once-daily regimens.

COMMENT

In this meta-analysis of clinical trials (none of which directly evaluated the effects of fixed-dose, single-tablet regimens), a lower pill burden was associated with both better adherence and better virologic outcomes. However, because the data analyzed were derived from clinical trials — where efforts to provide drugs and maximize follow-up are optimized — they may not be generalizable to clinical settings. Nonetheless, the findings have important implications: As antiretrovirals become generic, payers might elect to have patients "desimplify" their regimens — a change that, by increasing pill burden, could compromise adherence and outcomes. ***— Carlos del Rio, MD***

Nachega JB et al. Lower pill burden and once-daily antiretroviral treatment regimens for HIV infection: A meta-analysis of randomized controlled trials. **Clin Infect Dis** *2014 May 1; 58:1297.*

Lack of Drug Resistance in HIV Infection Despite PrEP: Can We Be Reassured?

Among 48 participants randomized to tenofovir/FTC preexposure prophylaxis who subsequently developed HIV infection, none demonstrated FTC- or tenofovir-associated mutations identifiable by clinical assays.

The iPrEx study established the efficacy of tenofovir/FTC for preexposure prophylaxis (PrEP) among men who have sex with men, but concern persists that HIV infection could occur with suboptimal PrEP use, resulting in the development of drug-resistant virus. In a subanalysis of the iPrEx study, researchers used clinical genotype and phenotype assays, deep sequencing, a novel allele-specific polymerase chain reaction (PCR) assay, and drug-exposure measurements to investigate drug resistance in participants who seroconverted during the trial.

After randomization, 131 participants (48 in the tenofovir/FTC arm, 83 in the placebo arm) developed incident infections; none showed major tenofovir- or FTC-specific mutations identifiable by clinical assays or reduced phenotypic susceptibility. Drug resistance to FTC (mutation M184V or I) did develop in the two participants who were placed on PrEP during unrecognized acute infection at study entry; isolates from both were hypersusceptible to tenofovir and FTC. Among the 48 tenofovir/FTC-arm participants who developed incident infections, none showed the tenofovir-associated mutations K65R or K70E above the biological cutoff, and two showed the M184I mutation at <1% (1 by deep sequencing, 1 by PCR).

Eight of the 48 tenofovir/FTC-arm participants with incident infections had detectable drug levels within 90 days of seroconversion (4 prior to but not at the seroconversion visit, 3 only at the seroconversion visit, 1 both prior to and at the seroconversion visit). In one participant with minor variant M184I, drug levels before seroconversion were undetectable in plasma and low but detectable in peripheral blood mononuclear cells, with values consistent with nondaily dosing.

COMMENT

Among iPrEx study participants who were randomized to tenofovir/FTC and seroconverted, detection of drug-resistance mutations was infrequent. The few mutations observed were FTC-associated and occurred primarily among those who initiated preexposure prophylaxis during acute infection. Incident infections occurred mainly in participants with irregular PrEP adherence; paradoxically, low drug exposure may have prevented the development of resistance mutations.

These results underscore the importance of baseline clinical and laboratory testing (i.e., HIV viral load assay) for high-risk individuals before PrEP is initiated to minimize the risk of starting it in an acutely infected patient. If acute infection is suspected in the setting of PrEP, prompt

evaluation by an HIV specialist is recommended to confirm this suspicion and determine the antiretroviral regimen that the patient should be started on for treatment.

— Carlos del Rio, MD

Note to readers: At the time NEJM Journal Watch reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

Liegler T et al. HIV-1 drug resistance in the iPrEx pre-exposure prophylaxis trial. **J Infect Dis** *2014 Apr 16; [e-pub ahead of print]. (http://dx.doi.org/10.1093/infdis/jiu233)*

Coronary Disease in Patients with HIV Infection: More than ART

HIV-infected individuals are at increased risk for noncalcified coronary plaques, with lower nadir CD4-cell counts and longer antiretroviral therapy duration being associated with coronary artery stenosis >50%.

Several studies have noted increased risk for coronary artery disease (CAD) and myocardial infarction in HIV-infected patients. This increase has been attributed to direct effects — or metabolic complications — of antiretroviral therapy (ART), factors associated with the virus itself (including chronic immune activation), or both. Surrogate markers of atherosclerotic disease have been used to further characterize this risk in HIV-infected patients.

Now, as part of the large, prospective Multicenter AIDS Cohort Study (MACS), researchers have used noncontrast cardiac computed tomography (CT) to measure coronary artery calcium (CAC) and CT angiography to assess plaque extent and characteristics. A total of 618 HIV-infected and 383 HIV-uninfected men who have sex with men underwent cardiac CT; 759 of the participants without contraindications to CT angiography also underwent this procedure. Data on CAD risk factors and HIV clinical variables were obtained from records for previous MACS visits.

In multivariate analyses adjusted for age, race, CT scanning center, cohort, and established CAD risk factors, the prevalence and extent of CAC were similar between HIV-infected and uninfected men. However, HIV-infected men had a significantly greater prevalence of plaque in any coronary segment and of noncalcified plaque, and a significantly greater extent of noncalcified plaque. In the HIV-infected group, lower nadir CD4-cell counts and longer ART duration were associated with coronary artery stenosis >50%.

COMMENT

Noncalcified plaque represents an early stage of plaque formation. Compared with calcified plaque, it may be more prone to rupture, the first step in the development of an acute coronary syndrome. The finding that HIV-infected individuals are at increased risk for noncalcified plaque suggests that the pathophysiology of plaque formation or progression may differ in this population. This study confirms similar observations in smaller ones, which have also shown an association between the presence of noncalcified plaque and markers of immune activation such as soluble CD163. These findings open the door for studies to further address the mechanisms leading to the increased risk for cardiac events in HIV-infected individuals, and to identify preventive strategies.

— Wendy S. Armstrong, MD

Dr. Armstrong is Medical Director of the Infectious Diseases Program at Grady Health System and Associate Professor of Infectious Diseases at Emory University School of Medicine, Atlanta. She reports no conflicts of interest.

Post WS et al. Associations between HIV infection and subclinical coronary atherosclerosis. **Ann Intern Med** *2014 Apr 1; 160:458.*

HIV Infection and Fracture Risk

A large case-control study conducted in a Northern European population showed an elevated fracture risk similar to that previously demonstrated in primarily North American populations.

HIV- and antiretroviral therapy–induced bone loss has long been recognized, but only recently have we begun to appreciate its effect on fracture risk. In a recent case-control study conducted to explore this association, researchers used Danish National Health Service registries data on patients with fractures in 2000 and age- and sex-matched controls without fractures that year (n=124,655 and 373,962, respectively).

After adjustment for traditional osteoporosis risks, HIV infection was associated with a significantly increased fracture risk (odds ratio, 2.00). This association was particularly strong at key fracture-prone sites, including the hip (OR, 6.46), the spine (OR, 4.65), and the forearm (OR, 2.34). The findings were similar between men and women and between younger and middle-aged populations. Risk was related to the duration of infection, rising most rapidly during the first 2 or 3 years following HIV diagnosis and more slowly thereafter.

COMMENT

One limitation of this work was lack of data to evaluate the effects of such confounding factors as CD4-cell counts, antiretroviral regimens, body-mass index, and smoking status. Nevertheless, this study involving a Northern European population confirms the findings of previous investigations of HIV-associated fracture risk (most of which have been conducted in North American populations).

The findings underscore the need for regular bone-disease screening in HIV-infected individuals as they age on antiretroviral therapy. The existing standard for managing bone disease is based on strategies developed for postmenopausal women, for whom therapy is delayed until osteoporosis develops. This approach may be suboptimal in the context of HIV-related bone loss, because the clinical definitions of osteoporosis are based on bone-mineral density (which often does not correlate with fracture risk in individuals aged <55 years — the age of most HIV-infected patients today).

Efforts are needed to understand the mechanism behind this phenomenon, and to develop an effective risk-assessment tool and therapeutic strategies for HIV-induced bone loss, to forestall what many fear to be an impending epidemic of fragility bone fracture in the aging HIV/AIDS population. ***— Igho Ofotokun, MD, MSc***

Dr. Ofotokun is an associate professor of infectious disease, Emory University School of Medicine, and an investigator for the Atlanta Clinical & Translational Science Institute, Emory University. He reports no conflicts of interest.

Prieto-Alhambra D et al. HIV infection and its association with an excess risk of clinical fractures: A nationwide case–control study. **J Acquir Immune Defic Syndr** *2014 May 1; 66:90.*

Insight into the Effect of Tenofovir in Patients with HBV/HIV Coinfection

Prior 3TC use, a higher baseline hepatitis B virus DNA level, and a lower nadir CD4 count were associated with decreased response to tenofovir.

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Reference: 1. Sterrantino G, Santoro L, Bartolozzi D, Trotta M, Zaccarelli M. Self-reported adherence supports patient preference for the single tablet regimen (STR) in the current cART era. *Patient Preference and Adherence* 2012; **6**:427-433.

S4 Tribuss®, Reg. No: 44/20.2.8/0980. Each film coated tablet contains 300 mg tenofovir disoproxil fumarate, 200 mg emtricitabine and 600 mg efavirenz. For full prescribing information, refer to the package insert approved by the medicines regulatory authority. Applicant: Pharmacare Limited. Co. Reg. No.: 1898/000252/06. Building 12, Healthcare Park, Woodlands Drive, Woodmead 2191. Tel (011) 239 3400, Fax (011) 239 3438. A16771 08/13.

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Reference: 1. Guidelines for antiretroviral therapy in adults. Southern African HIV Clinicians Society. *The Southern African Journal of HIV Medicine* 2012; 13(3):114-133.

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GUIDELINE WATCH

Use of Antiretroviral Drugs in Pregnancy

Specific drug information is updated, but the recommendations for treating neonates remain unchanged.

Sponsoring Organization: U.S. Department of Health and Human Services

Target Population: Primary care providers, obstetricians, pediatricians

Background and Objective

Increasing experience with older antiretrovirals (ARVs) and the availability of several new ones prompted a re-examination of these guidelines, which were last updated in July 2012. Recent reports of several HIV-infected neonates with good responses to nonstandard regimens were also considered.

Key Points and Recommendations

- All HIV-infected women who are contemplating pregnancy should be on a maximally suppressive ARV regimen.
- Neither tenofovir nor abacavir has to date been associated with excess risk for birth defects. Hence, these drugs and the combination pills containing them join AZT/3TC as viable nucleoside reverse transcriptase inhibitor options during pregnancy.
- Acceptable protease inhibitor components during pregnancy include ritonavir-boosted lopinavir or atazanavir, with boosted saquinavir or darunavir as alternatives.
- Despite long-standing concerns about the teratogenicity of efavirenz during the first trimester of pregnancy, the panel calls experience with the drug "reassuring" and concludes that it may be continued in women who become pregnant while virologically suppressed on an efavirenz-containing regimen. Nevirapine may also be continued in women doing well on the drug but should not be initiated in those with CD4 counts >250 cells/mm^3 or liver disease. There is still too little experience with etravirine and rilpivirine for these nonnucleoside reverse transcriptase inhibitors to be recommended for ARV-naive women during pregnancy.
- Raltegravir may be considered as an alternative agent in pregnancy. Dolutegravir and the elvitegravir-containing combination pill are not recommended for routine use in ARV-naive women during pregnancy because of a paucity of safety data. A similar caution still governs the use of enfuvirtide and maraviroc.
- Intrapartum intravenous AZT should be administered to women near delivery whose viral load is unknown, or is known to exceed >1000 copies/mL.
- HIV-exposed neonates should receive AZT for 4 to 6 weeks, with nevirapine added in the first few days of life if maternal infection is uncontrolled.
- The panel considered at length other ad hoc multidrug regimens for neonates that have been in the news recently, including the one inducing a "functional cure" in an infected neonate, and concluded that significant safety concerns mandate additional study before these regimens can be widely recommended.

COMMENT

Treatment of HIV-infected pregnant women is not just prevention of mother-to-child transmission, but also a valuable opportunity to initiate or optimize antiretroviral therapy in such women. These guidelines will continue to be refined as hands-on experience supplements laboratory data regarding the use of ART during pregnancy. ***— Abigail Zuger, MD***

Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 2014.

HBV therapies suppress HBV replication and can improve clinical outcomes but are rarely curative, so long-term treatment is needed. Most antiretroviral therapy (ART) regimens include two or three drugs with HBV activity (3TC, FTC, tenofovir), yet we have comparatively few data on HBV outcomes among patients on long-term ART. This issue is important, particularly because using 3TC or FTC alone for targeting HBV in coinfected patients often leads to development of HBV resistance. In a recent study involving HBV/HIV-coinfected CNICS-cohort patients who were taking a tenofovir-based regimen for ≥3 months and had on-treatment HBV DNA measurements, researchers examined factors potentially associated with subsequent HBV DNA suppression (defined as <1000 copies/mL).

Among the HBV/HIV-coinfected patients who met eligibility criteria (N=397; median age at tenofovir initiation, 40; 90% men; 51% white; 18% with hepatitis C virus coinfection; median nadir CD4 count, 128 cells/mm^3), 91% were also taking FTC or 3TC, 49% had 3TC exposure before tenofovir initiation, and 92% of those tested were hepatitis B e–antigen positive. In all, 192 patients (48%) achieved HBV suppression over a median of 28 months (17 months for 3TC-naive patients, 50 months for those with prior 3TC exposure). Prior 3TC exposure, baseline HBV DNA >50,000 copies/mL, and a lower nadir CD4-cell count were independently associated with a lower response to tenofovir.

COMMENT

This multicenter study, despite its retrospective, observational design, provides insight into contemporary clinical experience with HIV/hepatitis B virus–coinfected patients. It is noteworthy that only 48% of coinfected patients achieved HBV suppression, even though 91% were taking tenofovir together with 3TC or FTC. This finding underscores the importance of careful use of 3TC or FTC in HBV/HIV-coinfected individuals. It also strengthens the case for starting antiretroviral therapy early in such patients, with a regimen that includes two HBV-active drugs. ***— Keith Henry, MD***

Kim HN et al. Factors associated with delayed hepatitis B viral suppression on tenofovir among patients coinfected with HBV-HIV in the CNICS cohort. **J Acquir Immune Defic Syndr** *2014 May 1; 66:96.*

GUIDELINE WATCH

Managing Drug Interactions in the Treatment of HIV-Associated TB

These updated guidelines provide recommendations for managing drug interactions between rifamycin antibiotics and four classes of antiretrovirals and for co-treatment of tuberculosis and HIV infection in children and pregnant women.

Sponsoring Organization: CDC National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Division of Tuberculosis Elimination

Target Population: Primary care providers, HIV/tuberculosis (TB) treatment providers

Background and Objective

Co-treatment of TB and HIV infection is often complicated by adherence challenges, overlapping side effects, immune reconstitution inflammatory syndrome, and drug–drug interactions.

What's Changed

Recommendations for use of newer antiretrovirals, including CCR5-receptor antagonists and integrase inhibitors, are now provided. Other new features include the following:

- Summaries of clinical experience with use of specific antiretroviral therapy (ART) regimens during TB treatment, together with pharmacokinetic data
- A table summarizing clinical experience with key ART regimens and providing suggested regimens
- Recommendations on treatment for special populations (i.e., patients with latent TB infection, those with drug-resistant TB, young children, pregnant women)

Key Recommendations

- Efavirenz (600 mg for adults; standard weight-based dosing for children aged >3 years) plus two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), along with rifampin-based TB therapy, is the preferred strategy for co-treatment of HIV infection and TB.
- If efavirenz cannot be used (e.g., during the first trimester of pregnancy and in children aged <3 years), then a nevirapine- or protease inhibitor (PI)-based ART regimen can be used in combination with rifampin.
- Rifampin should not be coadministered with the second-generation nonnucleoside reverse transcriptase inhibitors (NNRTIs) rilpivirine or etravirine.
- High-dose lopinavir/ritonavir regimens should be used together with rifampin-based treatment only if hepatotoxicity is closely monitored.
- Patients who are unable to take NNRTIs can use rifampin in conjunction with triple- or quadruple-NRTI regimens if their HIV RNA levels are <100,000 copies/mL.
- Doubling the dose of raltegravir to 800 mg twice daily is recommended for adults taking rifampin, but this drug combination should not be used in individuals with high HIV viral loads.
- Although clinical data are limited, increasing the dose of maraviroc to 600 mg twice daily is recommended if the drug is coadministered with rifampin.
- A 150-mg daily dose of rifabutin, with careful monitoring for rifabutin-related toxicities, is recommended if this drug is coadministered with boosted PIs.
- Rifabutin can be used in patients on nevirapine-based ART and in those taking standard-dose raltegravir (400 mg twice daily).
- Nevirapine-based HIV treatment can be used in pregnant women receiving rifampin-based TB treatment. A nucleotide/nucleotide-only regimen with rifampin, or lopinavir/r with rifabutin, can also be considered for pregnant patients. More-frequent HIV RNA monitoring is recommended during pregnancy.
- For children on rifampin-based TB treatment, super-boosted lopinavir plus appropriate NRTIs is recommended. Alternatives include standard-dose efavirenz–based ART for children aged >3 years and a triple-nucleoside regimen for those aged <3 years.

COMMENT

These revisions provide long-awaited clarity on the coadministration of antiretrovirals, especially nonnucleoside reverse transcriptase inhibitors, and tuberculosis treatment. Although studies have shown a highly variable effect of rifampin on efavirenz concentrations, the recommendation of a 600-mg dose balances the needs for maintaining therapeutic levels of efavirenz and reducing the risk for neurological side effects. The doses of raltegravir and maraviroc that should be used in conjunction with TB treatment are clarified. Finally, helpful guidance (including the use of super-boosted lopinavir) is provided for co-treatment of HIV infection and TB in children.

— Salim S. Abdool Karim, MD, PhD

Centers for Disease Control and Prevention (CDC). Announcement: Updated guidelines on managing drug interactions in the treatment of HIV-related tuberculosis. **Morb Mortal Wkly Rep MMWR** *2014 Mar 28; 63:272.*

Centers for Disease Control and Prevention (CDC). Managing drug interactions in the treatment of HIV-related tuberculosis. June 2013.

Hepatitis Delta Virus Coinfection: A Major Cause of Hepatic Decompensation and Death

HDV coinfection is not rare among HIV-infected individuals and is associated with elevated rates of liver-related events.

Hepatitis delta virus (HDV) is a small RNA virus that replicates only in the presence of hepatitis B virus (HBV) infection. Because HDV is transmitted in the same ways as HBV, HDV infection is not rare among HIV/HBV-coinfected individuals. To assess the effects of hepatitis virus coinfections on liver-related outcomes among HIV-infected individuals, investigators in Spain retrospectively analyzed data from a cohort of 1147 patients (81% male; mean age, 42; 46% injection-drug users; 85% on antiretroviral therapy) followed since 2004 at an HIV clinic in Madrid.

At study entry, 45% of participants were hepatitis C virus (HCV)-antibody positive, 7% were HBsAg positive, and 1.5% were HDV-antibody positive. Of 521 HCV-coinfected patients, 21 cleared HCV spontaneously during the study period, and 233 were treated with interferon-based therapy; 106 of the latter group achieved sustained virologic response. During a mean follow-up of 81 months, 15 patients died of liver-related conditions (cirrhosis in 6, hepatocellular carcinoma in 5, variceal bleeding in 3, hepatorenal syndrome in 1), and 26 had first episodes of liver decompensation (ascites in 16, variceal bleeding in 6, hepatocellular carcinoma in 5). Compared with HIV monoinfection, HIV infection with HBV/HDV coinfection and baseline liver stiffness were independently associated with higher liver-related morbidity and mortality. For HIV/HCV-coinfected patients who achieved HCV clearance spontaneously or following antiviral therapy, duration of event-free survival was similar to that of HIV-monoinfected controls.

COMMENT

In this study, coinfection with hepatitis D virus was associated with hepatic decompensation and death from liver-related causes, although it should be noted that most of the participants were male, and a high proportion of them used injection drugs, abused alcohol, or both — factors known to be associated with worse outcomes, regardless of HDV infection. Nonetheless, because no effective therapy currently exists for HDV infection, all HIV-infected individuals who are not immune to hepatitis B should receive the HBV vaccine, and those who have active HBV infections should be treated with antivirals. Another important finding is that patients with HCV infection who achieved a sustained virologic response following treatment with an interferon-based therapy were at no higher risk for liver-related events than HIV-monoinfected patients. ***— Carlos del Rio, MD***

Note to readers: At the time NEJM Journal Watch reviewed this paper, its publisher noted that it was not in final form and that subsequent changes might be made.

Fernández-Montero JV et al. Hepatitis delta is a major determinant of liver decompensation events and death in HIV-infected patients. **Clin Infect Dis** *2014 Mar 14; [e-pub ahead of print]. (http://dx.doi.org/10.1093/cid/ciu167)*

Improving HIV Treatment Outcomes During Incarceration

Incarceration offers the opportunity to improve treatment outcomes of HIV-infected detainees.

The epidemic of incarceration in the U.S., like the HIV epidemic, disproportionately affects blacks — particularly black men, who have more than a one in four chance of being incarcerated at some point in life. It is thus not surprising that one sixth of HIV-infected individuals cycle through correctional facilities annually and that HIV prevalence among inmates is threefold higher than in the community. HIV-infected prison inmates receive medical care, including antiretroviral therapy (ART), but what are the outcomes of such treatment?

To explore this question, investigators conducted a retrospective review involving individuals incarcerated in a Connecticut Department of Correction facility for ≥90 consecutive days between March 1, 2005, and June 29, 2012. Among 882 HIV-infected detainees receiving ART in prison (mean age, 43; 81% men; 48% black; total, 1185 incarceration periods), only 30% had viral suppression (<400 copies/mL) and 6% had undetectable viral loads (<50 copies/mL) at intake, yet 70% and 23%, respectively, had achieved these goals by the time of release. Similarly, mean CD4 count increased during incarceration by 98 cells/mm^3. Pre-release virologic suppression was associated with female sex and lower severity of psychiatric disorder.

COMMENT

Incarceration is an opportunity to optimize outcomes of therapy and achieve virologic suppression for detainees with HIV infection. The challenge lies in maintaining those improved HIV outcomes through effective linkage to follow-up HIV and mental health care. ***— Carlos del Rio, MD***

Meyer JP et al. Optimization of human immunodeficiency virus treatment during incarceration: Viral suppression at the prison gate. **JAMA** *2014 May; 174:721.*

Substance Use May Impair HIV Control

Use resulted in missed appointments and lower rates of virologic suppression.

Among HIV-infected patients, blacks have worse outcomes than whites — a fact that has been documented repeatedly yet never adequately explained. Researchers sought to explore the association by quantitating the effects of problematic alcohol/drug use and treatment for substance use on appointment-keeping and virologic suppression among black patients receiving care at a Birmingham, Alabama, clinic.

Most of the 576 participants were male and were newly enrolled in the clinic. At interview, 50% were uninsured, 64% reported "mental health issues," 34% reported problematic alcohol or drug use during the preceding year, 19% reported long-term at-risk drug or alcohol use, and 13% were receiving or had recently received substance use treatment. The median CD4 count was 321 cells/mm^3.

During the 2 years after the interview, the median proportion of scheduled appointments attended was 82%, and the median proportion of RNA assessments showing virologic suppression was 71%. Active substance use reduced rates of appointment keeping, both for patients in drug treatment and for those not in treatment; it also reduced the likelihood of virologic suppression but only among those not in treatment. These associations all lost statistical significance when adjusted for other variables such as age, mental health status, and longtime drug or alcohol use.

COMMENT

These data imply that when substance use is not directly addressed with efforts at treatment, HIV control may suffer — an association that, these researchers posit,

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may explain some of the race-based differences in HIV treatment outcomes. However, as the statistics make clear, this subject is so complicated, and so many different variables may involved, that the conclusions may or may not be relevant to the individual patient. ***— Abigail Zuger, MD***

Howe CJ et al. The role of at-risk alcohol/drug use and treatment in appointment attendance and virologic suppression among HIV+ African Americans. **AIDS Res Hum Retroviruses** *2014 Mar; 30:233.*

Case Report of Female-to-Female HIV Transmission

Phylogenic analysis and history confirm that a newly HIV-infected female acquired the virus from her female partner.

Female-to-female transmission of HIV has been reported but is difficult to verify. The CDC now reports the case of a newly HIV-infected, 46-year-old woman with three female sexual partners in the preceding 5 years. This patient had no history of tattoos, injection-drug use, acupuncture, transfusions, transplants, or any other known HIV risk factors. She had sold plasma regularly, with the last (negative) HIV test performed in March 2012. Ten days later, she presented to an emergency room with fever, sore throat, gastrointestinal complaints, dry cough, and muscle cramps. HIV enzyme immunoassay results (EIA) were negative, and she was treated with azithromycin. Eighteen days after that, she attempted to sell plasma again but was refused due to positive HIV EIA results (confirmed by Western blot positivity).

Her partner was a 43-year-old woman who received a diagnosis of HIV infection and AIDS in 2008, at which point she had a viral load of 82,000 copies/mL. She began antiretroviral therapy in February 2009 and initially showed a good response, but stopped in November 2010 and was lost to follow-up in January 2011. The couple reported unprotected oral and vaginal contact, including during menses, and use of insertive sex toys shared between them but not with other partners. The recently infected woman reported that her partner was her only sexual contact for the 6 months preceding seroconversion. Phylogenetic analysis of HIV isolates from the two women found 98% pairwise nucleotide sequence homology for both the *env* and *pol* regions, with numerous shared polymorphisms.

COMMENT

The information provided on this case supports the conclusion that, although extremely rare, female-to-female HIV transmission is possible. The scenario also highlights many of the tenets of HIV prevention: the importance of linkage to care, achieving viral suppression, maintaining linkage and suppression, sharing HIV status with sexual partners, minimizing exposure to blood and body fluids (particularly from a patient without full viral suppression on antiretroviral therapy), and — if engaging in risky behaviors with an HIV-infected person not on suppressive ART — potential use of pre-exposure prophylaxis. ***— Keith Henry, MD***

Chan SK et al. Likely female-to-female sexual transmission of HIV — Texas, 2012. **MMWR Morb Mortal Wkly Rep** *2014 Mar 14; 63:209.*