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## Recent Outbreak of HIV and HCV Infections with Injection Drug Use

The Indiana State Department of Health (ISDH) and the Centers for Disease Control and Prevention (CDC) revealed a recent and rapid spread of human immunodeficiency virus (HIV) infection in a small rural community in Indiana. In the United States, there are approximately 50,000 new cases of HIV infections diagnosed each year, of which an estimated eight percent are due to injection drug use. In Indiana, however, 135 people were newly diagnosed with HIV in about a six-month time period, of which about 96 percent were among persons who inject drugs (PWID) and who reported using shared equipment to dissolve and inject prescription-type oxymorphone (Opana® ER) tablets.

In addition, rates of hepatitis C virus (HCV) infection are increasing in the U.S., particularly among young, non-urban PWID who abuse prescription-type opioids. The CDC published a health advisory describing this recent outbreak and urge immediate action to prevent further HIV and HCV transmission and to control similar outbreaks in other communities.

Health departments should assess recent increases in the number of HIV infections due to injection drug use; the number of new HCV infections, especially among those 35 years of age and younger; and prescription-type opioid drug abuse, overdose, drug treatment admissions, and drug arrests. People actively injecting drugs or who are at high risk should have access to integrated prevention services that include HIV and HCV infection screening; substance abuse services; counseling against the use of shared needles and syringes; access to sterile injection equipment; and access to HIV pre-exposure prophylaxis for at risk HIV-negative individuals or post-exposure prophylaxis for those potentially exposed to HIV within the past 72 hours. Healthcare providers should ensure that patients who are HIV and/or HCV infected adhere to prescribed therapy and receive ongoing care. State and local health departments and the CDC should be notified of suspected clusters of recent HIV or HCV infection.

## FDA's Final Industry Guidance on Abuse-Deterrent Opioids

Abuse and misuse of opioid medications is a serious and growing public health concern and the FDA considers the development of abuse-deterrent products a high priority. Opioid products are often manipulated to circumvent extended-release (ER) properties. For example, oral tablets may be crushed and then snorted, smoked, or dissolved and injected.

Most available abuse-deterrent technologies are intended to make drug manipulation more difficult or to make abuse of the manipulated drug less attractive or less euphoric. Abuse-deterrent technologies are rapidly evolving. To aid industry, the FDA has issued final guidance on developing opioid drug products with abuse-deterrent properties.

In their article, "Guidance for Industry: Abuse-Deterrent Opioids – Evaluation and Labeling", the FDA explains their current view on the evaluation of abuse-deterrent formulations. The agency advises drug manufacturers to anticipate that deterring abuse by one route may shift abuse to another route and should assess if deterrent effects will have a meaningful impact on the overall abuse of the product. Additionally, the study sponsor should compare their product to appropriate abuse-deterrent and non-abuse-deterrent products that are currently available. The FDA outlines four categories of studies. Three types of premarketing studies include: 1) laboratory-based *in vitro* studies to evaluate the ease with which the abuse-deterrent formulation

### Drug Information Highlights

- The FDA issued a safety communication strengthening its warning of potentially fatal hypersensitivity reactions associated with the iron replacement drug ferumoxytol (Feraheme®; AMAG). Ferumoxytol is given intravenously (IV) to treat iron-deficiency anemia. In addition to a boxed warning for this reaction, the labeling indicates that the drug is contraindicated in patients who have had an allergic reaction to any IV iron replacement product.
- Regeneron's aflibercept (Eylea®) intravitreal injection gained an expanded indication for the treatment of diabetic retinopathy in patients with diabetic macular edema. Aflibercept is also approved for the treatment of neovascular (wet) age-related macular degeneration, macular edema following retinal vein occlusion, and diabetic macular edema.
- Diltiazem extended-release tablets (Cardizem® LA; Valeant) received approval to improve exercise tolerance in patients with chronic stable angina. The product is also indicated for the treatment of hypertension.
- Filgrastim (Neupogen®; Amgen) injection has been approved to increase survival in patients acutely exposed to myelosuppressive doses of radiation. Filgrastim is also indicated for use in patients with cancer receiving myelosuppressive chemotherapy, patients undergoing bone marrow transplantation or autologous peripheral blood progenitor cell collection and therapy, and in patients with congenital, cyclic or idiopathic neutropenia.
- AbbVie's ribavirin tablets (Moderiba™) have received approval for the treatment of chronic HCV infection in patients five years of age and older who have compensated liver disease and have not previously received treatment with interferon alfa. Moderiba was previously indicated for use in adults only.
- The FDA has expanded the monotherapy use of Upsher-Smith's topiramate extended-release capsules (Qudexy™ XR) to include patients ages two years to less than ten years with partial onset seizures (POS) or primary generalized tonic-clonic seizures. Qudexy XR is also indicated in this age group as adjunctive therapy for POS, primary generalized tonic-clonic seizures and seizures associated with Lennox-Gastaut syndrome.

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can be compromised; 2) studies to assess how the pharmacokinetics of a product contribute to abuse potential; and 3) randomized, double-blind, placebo-controlled and positive-controlled crossover studies conducted in a drug-experienced, recreational user population to evaluate the “drug-liking” potential of the product. The fourth type of study is a postmarketing study to determine if the product with abuse-deterrent properties resulted in meaningful reductions in abuse, misuse, addiction, overdose, and death.

The FDA advises that the drug label should describe the formulation’s specific abuse-deterrent properties as well as the specific routes of abuse that the product has been developed to inhibit. It is anticipated that abusers will be able to overcome a technology such that it no longer has a meaningful effect on deterring abuse, at which time the FDA may require label revisions.

While the development of abuse-deterrent technologies is encouraged, the FDA states that it is important that opioids without abuse-deterrent properties remain available for use in some clinical settings, such as for patients in hospice care or with difficulty swallowing.

This guidance does not address the development or testing of generic formulations of abuse-deterrent opioid products; however, the FDA plans to address abuse-deterrent generics in the future.

- AstraZeneca’s ticagrelor (Brilinta®) tablets are now approved to be crushed and mixed in water and given orally or via a nasogastric tube for patients with acute coronary syndrome (ACS) who are unable to swallow tablets whole. Ticagrelor is a P2Y<sub>12</sub> platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with ACS.

#### Pipeline News: Upcoming Prescription Drug User Fee Acts (PDUFA) Dates

- **2nd Quarter 2015:** cariprazine, oral dopamine receptor partial agonist; manic/mixed treatment of bipolar disorder, schizophrenia; Gedeon Richter USA/Actavis.
- **2nd Quarter 2015:** MuDelta; eluxadolone; oral Mu and Delta opioid receptor agonist; diarrhea predominant irritable bowel syndrome (IBS-D); Actavis.
- **May 27, 2015:** Xifaxan®; rifaximin; oral antibacterial; IBS-D; Salix.

### Updated Guidelines for the Use of ART in Adults and Adolescents

On April 8, 2015, the Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents released updated Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents. The guidelines support the 2014 Centers for Disease Control and Prevention (CDC) testing algorithm, which recommends use of the recently approved combination immunoassays that detect HIV-1 and HIV-2 antibodies and HIV-1 p24 antigen for screening of HIV infection. Antiretroviral therapy (ART) is recommended for all individuals with HIV-1 infection and should be offered to those with early HIV-1 infection. The Panel recommends five regimens for patients who are naïve to ART, which includes four integrase strand transfer inhibitor (INSTI)-based regimens and one ritonavir-boosted protease inhibitor (PI/r)-based regimen.

INSTI-based regimens:

- dolutegravir/abacavir/lamivudine (Triumeq®; ViiV) – for patients who are HLA-B\*5701 negative only
- dolutegravir (Tivicay®; ViiV) plus tenofovir/emtricitabine (Truvada®; Gilead)
- elvitegravir/cobicistat/tenofovir/emtricitabine (Stribild®; Gilead) – for patients with pre-ART creatinine clearance greater than 70 mL/min only
- raltegravir (Isentress®; Merck) plus tenofovir/emtricitabine (Truvada)

Ritonavir-boosted regimen:

- darunavir (Prezista®; Janssen)/ritonavir (Norvir®; AbbVie) plus tenofovir/emtricitabine (Truvada)

Due to the protease inhibitors high genetic barrier to resistance, a PI/r-based regimen is preferred for patients who are likely to be nonadherent to therapy or who have NRTI drug resistance.

Several regimens that were previously listed among recommended regimens are now listed as alternative regimens due to reasons such as less desirable tolerability or toxicity profiles.

For the management of ART-experienced patients, guidance in ART prescribing is detailed for several clinical scenarios including first-line and second-line failures. Although rare, new-onset central nervous system (CNS) symptoms can indicate breakthrough of HIV infection within the CNS, despite plasma HIV RNA suppression; guidance on the evaluation of CNS signs and symptoms is provided.

A section has been added discussing the impact of persistently low CD4 cell count (< 200 cells/mm<sup>3</sup>) and persistent inflammation on morbidity and mortality. Therapy intensification by adding antiretroviral (ARV) drugs or switching ARV drug classes does not consistently improve CD4 cell recovery or reduce immune activation and is not recommended; therefore no interventions to increase CD4 cell counts and/or decrease immune activation are currently recommended. Strategies to reduce risk factors such as smoking cessation, healthy diet and exercise, and managing chronic comorbidities, such as hypertension, hyperlipidemia, and diabetes are advised.

The discussion on HIV/Hepatitis C (HCV) coinfection has been updated to include the new combination HCV antiviral product obitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak™; AbbVie) and its concomitant use with ART. Revisions to the drug interaction tables have been made and include ritonavir- and cobicistat-boosted regimens. This section provides pertinent mechanisms for drug interactions relating to ARV pharmacokinetics.

## Recent FDA Approvals

Generic Name	Trade Name	Description	Applicant	FDA Status
deferasirox	Jadenu™	The iron chelator, deferasirox (Jadenu), received accelerated approval for the treatment of chronic iron overload due to blood transfusions in patients two years of age and older and for the treatment of chronic iron overload in patients ten years of age and older with non-transfusion-dependent thalassemia (NTDT) syndromes and with a liver iron (Fe) concentration (LIC) $\geq 5$ mg Fe per gram of dry weight (Fe/g dw) and a serum ferritin $> 300$ mcg/L. FDA approvals were based on a reduction of liver iron concentrations and serum ferritin levels. Continued approval for these indications may be contingent upon verification and description of clinical benefit reported in confirmatory trials. Contraindications for use include serum creatinine greater than twice the upper limit of normal (ULN) for the patient's age, creatinine clearance $< 40$ mL/min, poor performance status, high-risk myelodysplastic syndromes, advanced malignancies, platelet levels $< 50 \times 10^9/L$ , and known hypersensitivity to any component of the product. Labeling includes a boxed warning regarding the risks of renal and hepatic failure and gastrointestinal hemorrhage. Deferasirox is available in 90 mg, 180 mg, and 360 mg oral tablets. Recommended initial dosages are 14 mg/kg once daily for transfusional iron overload and 7 mg/kg for NTDT with doses calculated to the nearest whole tablet.	Novartis	FDA NDA priority approval 3/30/2015
albuterol sulfate	ProAir® RespiClick	The FDA approved ProAir RespiClick, an albuterol sulfate breath-actuated inhalation powder for the treatment or prevention of bronchospasm with reversible obstructive airway disease and the prevention of exercise induced bronchospasm in patients 12 years of age and older. Pharmacokinetic and safety profiles are similar to that of ProAir HFA. Each RespiClick device delivers 108 mcg of albuterol sulfate per actuation for a total of 200 doses. Launch is expected in the second quarter of 2015.	Teva	FDA NDA approval 3/31/2015
ivabradine	Corlanor®	Ivabradine (Corlanor) is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction $\leq 35\%$ , who are in sinus rhythm with resting heart rate $\geq 70$ beats per minute (bpm) and who are either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use. Its use is contraindicated in patients with acute decompensated heart failure, blood pressure $< 90/50$ mmHg or resting heart rate $< 60$ bpm, sick sinus syndrome, sinoatrial block, third degree atrioventricular block, severe hepatic impairment, and pacemaker dependence. Ivabradine is available as 5 mg and 7.5 mg oral tablets. Recommended starting dose is 5 mg twice daily which can be increased after 2 weeks based on heart rate to a maximum of 7.5 mg twice daily. Common adverse effects include bradycardia, hypertension, and atrial fibrillation.	Amgen	FDA NDA priority approval 4/15/2015
glatiramer acetate	Glatopa™	The FDA approved glatiramer acetate (Glatopa) 20 mg/1 mL single-dose prefilled syringe for the once-daily treatment of relapsing-forms of multiple sclerosis. It is a therapeutically equivalent generic to Copaxone® by Teva. Copaxone is also available as a 40 mg/mL single-dose prefilled syringe for three times per week dosing, a regimen that has no FDA approved generic equivalent. Both the 20 mg/mL and the 40 mg/mL formulations are given subcutaneously and are not interchangeable.	Sandoz	FDA aNDA approval 4/16/2015
nebivolol hydrochloride	no trade name	The first generic version of nebivolol hydrochloride oral tablets the generic for Bystolic® a beta-adrenergic blocker indicated for the treatment of hypertension, have been approved. Tablets will be available as 2.5 mg, 5 mg, 10 mg, and 20 mg strengths.	Amerigen	FDA aNDA approval 4/16/2015
aripiprazole	no trade name	The first generic version of aripiprazole, equivalent to Abilify®, has been FDA approved. Aripiprazole is an atypical antipsychotic agent indicated for the management of schizophrenia, bipolar I disorder, Tourette's disorder, irritability associated with autistic disorder, and as adjunctive treatment for major depressive disorder. Aripiprazole will be available as 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg tablets and 10 mg and 15 mg orally disintegrating tablets.	Alembic, Hetero, Teva, Torrent	FDA aNDA approval 4/28/2015

### References

<https://www.magellanmedicaid.com/news/clinicalalerts.asp>  
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