Published in final edited form as:

Crit Care Med. 2018 May ; 46(5): 663–665. doi:10.1097/CCM.0000000000003048.

Management of Antiretrovirals in Critically Ill Patients: Great Progress but Potential Pitfalls

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Keywords

HIV; Antiretroviral therapy

In the 1980s and 1990s, HIV infection inevitably (with a few rare exceptions) led to multiple opportunistic complications and premature death. Pneumocystis pneumonia, toxoplasma encephalitis, cryptococcal meningitis, CMV retinitis, pneumococcal bacteremia, Kaposi sarcoma, and lymphoma were recurrent complications that led most patients to die within a decade of their initial AIDS diagnosis. These opportunistic processes still occur in persons who are not aware of their HIV infection, or persons who are not taking antiretroviral therapy (ART) due to social, economic, or mental health challenges.

In this current decade, the prospects for persons with HIV infection are much more sanguine. About half of the 1.1 million persons living in the US have achieved the effective, long term HIV suppression the correlates with prolonged survival (1–3). The number of persons living with HIV in the United States is not likely to fall in the next decade; since in 2014 there were 37,600 new cases of HIV infection and 6,721 deaths, a net gain of over 30,000 prevalent cases. Moreover, the life expectancy of persons with HIV infection who are successfully treated with ART is projected to exceed 70 years suggesting that such HIV-infected persons will have almost normal life expectancies, although that life expectancy may be affected by specific HIV-related morbidities (2).

With at least 600,000 persons with HIV on effective long term ART in the United States (3), intensivists can expect to see HIV-infected patients in their ICUs for trauma, post-operative care, routine medical maladies, and the expected consequences of aging. HIV-infected persons on effective ART may in fact be overrepresented in ICUs because they have more than the expected morbidities due to their “accelerated aging,” which is a consequence of

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Reprints: We do not plan on ordering reprints of the manuscript

Conflicts of Interest: No author has a conflict of interest to report.

low level chronic HIV viremias (despite ART) that produces an ongoing state of enhanced inflammation. This enhanced inflammation accelerates their development of cardiovascular, cerebrovascular, hepatic, renal and malignant neoplastic diseases (4).

Principles of ART in critically ill patients

The miraculous development of highly effective antiretrovirals has transformed HIV infection from an inevitably fatal disease to a chronic process with an almost normal quality of life. The U.S. Food and Drug Administration has approved more than two dozen separate drugs (representing 6 different drug classes) and 15 drug combinations for HIV therapy (5). However, these advances have been associated with added levels of complexity regarding their use, especially in critically ill patients, because of multiple drug interactions and the risks associated with either starting, stopping or inappropriately dosing these therapies. As such, management decisions regarding ART are increasingly complex: infectious disease physicians and pharmacists can often add considerable strategic expertise to decisions in the ICU about the initiation, continuation, or discontinuation of ART.

Avoiding the Development of Resistance to ART

Starting or discontinuing ART can have lifelong consequences for the patient in terms of promoting the emergence of antiretroviral drug resistance. Once HIV becomes resistant to a drug or drug class, that resistance persists lifelong. Virtually all commonly used antiretroviral drugs are only available as oral formulations. Administration by this oral route in critically ill patients can lead to sub-therapeutic drug levels and lifelong antiretroviral resistance. This lifelong resistance occurs because, mutations in this DNA virus become archived in cellular DNA. Crushing tablets to put them down feeding tubes presents multiple additional dimensions of unpredictable delivery and absorption. Thus, in patients who are post-operative, or patients who are intubated, maintaining predictable and adequate plasma levels of drugs poses a challenge. Strategies to maintain appropriate drug levels are important to attempt. However, in some situations involving uncertain gastrointestinal absorption that is likely to persist over several days or more, or inability to administer oral agents even through a feeding tube, ART should be stopped altogether since the absence of drug removes the selective pressure which drives antiretroviral resistance. While there are a wider variety of drugs available with different mechanisms of action compared to 15 years ago, patients who will be on lifelong ART for decades cannot afford to lose whole classes of drugs due to suboptimal therapeutic decisions. Stopping drugs to prevent the emergence of resistance, however, can be challenging and should be assessed on a case-by-case basis. Discontinuation of multidrug or single tablet regimens when the individual component drugs have different half-lives can lead to periods when only one drug has measurable plasma levels, again increasing the probability of creating lifelong resistance. This problem is most notorious for Atripla® (the combination oral tablet of efavirenz, tenofovir disoproxil, and emtricitabine) since the efavirenz component has a longer half-life (55 hrs) compared to tenofovir (17 hrs) or emtricitabine (10 hrs). Thus, if Atripla® is stopped, patients effectively receive efavirenz monotherapy for many days after the tenofovir and emtricitabine have been eliminated. This unintended monotherapy promotes the emergence of resistance even over a

period of days. There is not, however, a validated and standardized strategy to minimizing this risk, but some plausible approach needs to be used.

There is the prospect that an injectable antiretroviral regimen may be available in the future. Long-acting intramuscular injections of cabotegravir and rilpivirine are currently being studied as every 4 or 8 weeks injections for chronic maintenance therapy. However, the safety, efficacy, pharmacokinetics, and potential drug interactions of such regimens in critically ill patients needs to be carefully studied before they can be recommended for use in an ICU (6).

Life-Threatening Complications of ART

Of the antiretroviral agents recommended in current guidelines, most are extremely well tolerated, but some serious complications may develop that could lead to ICU admission. Fortunately many of the most toxic drugs in the 1990s, such as didanosine (DDI) or stavudine (D4T), that were associated with pancreatitis, neuropathy, and/or lactic acidosis are no longer marketed in the United States (7). More effective and less toxic options have been developed.

Two currently used drugs deserve special mention whether these drugs are used alone or in combination tablets. Abacavir can cause distributive shock that may present like sepsis. This complication occurs exclusively in those patients expressing HLA-B*5701. This syndrome is less likely to occur when providers test patients for HLA-B*5701 prior to therapy, but some providers may have prescribed these drugs without taking this precaution. Within six weeks of starting this drug, patients can present with a non-specific febrile illness that includes fatigue, nausea, vomiting, pulmonary infiltrates, and/or skin rash (8). Some patients stop taking their abacavir due to nausea or malaise, but then restart the drug when they feel better. This “re-challenge” can elicit a severe hypersensitivity reaction that causes distributive shock and bronchospasm that has been associated with fatal outcomes (9). Therapy is supportive after the drug is stopped.

Raltegravir has been associated with rhabdomyolysis which has occurred as early as ten days and as late as 22 months after initiation of therapy. To date, these episodes have not been fatal, but creatinine kinase rises can be substantial (10, 11). It remains to be seen whether this syndrome is specific for this particular drug, or whether this is a class-related phenomenon which will be observed with all of these agents which currently dominate the preferred regimens that guidelines recommend.

Drug Interactions Associated with ART

The CYP450 enzyme system is the most common pathway for hepatic metabolism of drugs, affecting many drugs that are used in the ICU, including certain sedatives, hypnotics, anticonvulsants, anticoagulants, antiarrhythmics, analgesics, and antipsychotics. While many types of drug interactions involving ART can occur, the most prominent involve CYP450 inhibitors. Two components of certain combination tablets, i.e., cobicistat and ritonavir, are included in some ART combination tablets, not for their antiretroviral activity but for their ability to enhance the pharmacokinetics of certain antiretrovirals by inhibiting CYP3A4.

While they are very effective in optimizing the pharmacokinetics of ART, they also have substantial boosting effects on many other drugs, including sedatives, analgesics, anticoagulants, antipsychotics, anticonvulsants, and antiarrhythmics. Thus, if these medications are administered in the ICU to patients who are on protease inhibitors cobicistat, or ritonavir containing ART, exaggerated effects of the target drugs and/or enhanced toxicities may occur (Supplementary Table 1).

Efavirenz is an example of another antiretroviral agent that can cause complicated drug interactions as it can induce the metabolism of medications which are metabolized via CYP3A4. For instance, efavirenz containing ART (i.e., Atripla) can decrease (rather than increase) the systemic exposure of anticonvulsants (i.e., carbamazepine, phenytoin) since it is an inducer of CYP3A4. Thus, if efavirenz is introduced to a patient on a stable anticonvulsant regimen containing carbamazepine or phenytoin, the metabolism of the anticonvulsant is induced, and efficacy could be compromised. By the same mechanism, anticonvulsants can also decrease plasma levels of efavirenz as they too are inducers of CYP3A4 (12).

Table 1 provides examples of drug interactions. Such interactions are also described online in more detail (7).

Conclusion

The astonishing development of effective and durable ART over the past 20 years has provided an opportunity for HIV-infected persons to attain the life expectancy of their HIV-uninfected counterparts. Maintaining the activity of these lifesaving regimens requires strategic decisions about drug absorption, drug-drug interactions, pharmacokinetics, and the advantages of disadvantages of drug induced modulation of inflammatory and immunologic responses. Optimizing patient safety requires recognition of the toxicities of these agents as well. Critical care is a team endeavor, and management of ART is yet another example of the benefits of close collaboration between intensivists and their infectious disease and pharmacy colleagues.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial Support: This work was supported by intramural funding from the National Institutes of Health.

References

1. Centers for Disease Control and Prevention. [Accessed November, 2017] HIV Continuum of Care, U.S., 2014, Overall and by Age, Race/Ethnicity, Transmission Route and Sex. 2017. Available at: <https://www.cdc.gov/nchhstp/newsroom/2017/HIV-Continuum-of-Care.html>
2. Lohse N, Obel N. Update of Survival for Persons With HIV Infection in Denmark. *Ann Intern Med*. 2016; 165:749–750. [PubMed: 27842400]
3. [Accessed November, 2017] Understanding the HIV Care Continuum. 2017. Available at: <https://www.cdc.gov/hiv/pdf/library/factsheets/cdc-hiv-care-continuum.pdf>

4. Neuhaus J, Jacobs DR Jr, Baker JV, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. *J Infect Dis*. 2010; 201:1788–1795. [PubMed: 20446848]
5. [Accessed October 29, 2017] Antiretroviral drugs used in the treatment of HIV infection. Available at: <https://www.fda.gov/ForPatients/Illness/HIVAIDS/Treatment/ucm118915.htm>
6. Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. *Lancet*. 2017; 390:1499–1510. [PubMed: 28750935]
7. Department of Health and Human Services. [Accessed November, 2017] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. 2017. Available at: <https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf>
8. Hetherington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. *Clin Ther*. 2001; 23:1603–1614. [PubMed: 11726000]
9. Hewitt RG. Abacavir hypersensitivity reaction. *Clin Infect Dis*. 2002; 34:1137–1142. [PubMed: 11915004]
10. Croce F, Vitello P, Dalla Pria A, Riva A, Galli M, Antinori S. Severe raltegravir-associated rhabdomyolysis: a case report and review of the literature. *Int J STD AIDS*. 2010; 21:783–785. [PubMed: 21187364]
11. Lee FJ, Amin J, Bloch M, Pett SL, Marriott D, Carr A. Skeletal muscle toxicity associated with raltegravir-based combination antiretroviral therapy in HIV-infected adults. *J Acquir Immune Defic Syndr*. 2013; 62:525–533. [PubMed: 23274936]
12. Sustiva - Highlights of prescribing information. [Accessed November 1, 2017] Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020972s033,021360s0211bl.pdf