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Tolerability of Postexposure Antiretroviral Prophylaxis for Occupational Exposures to HIV

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Abstract

A substantial body of evidence provides support (but not definitive proof of efficacy) for the use of antiretroviral agents as postexposure prophylaxis for occupational exposures to HIV in the healthcare workplace. Despite the lack of definitive evidence of the efficacy of these agents in this setting, over the past decade this intervention has become the standard of care for healthcare workers who sustain occupational exposures to HIV.

Administration of these agents – even for a relatively short 28-day postexposure course – is often fraught with difficulty. All of the agents currently used for postexposure prophylaxis regimens have substantial adverse effects, and significant adverse effects occur in more than two-thirds of individuals electing prophylaxis. This manuscript reiterates current US Federal Government guidelines for the administration of postexposure prophylaxis, specifically noting that zidovudine plus lamivudine (with or without a protease inhibitor) remains the recommended regimen. The paper summarises the significant toxicities associated with nucleoside reverse transcriptase inhibitors (primarily nausea, vomiting, diarrhoea and bone marrow suppression), non-nucleoside reverse transcriptase inhibitors (rash, fever, gastrointestinal symptoms and hepatitis, including hepatic decompensation necessitating liver transplantation) and protease inhibitors (nausea, vomiting, diarrhoea, abdominal pain, hyperglycaemia, hyperlipidaemia, headache and anorexia).

As a class, the antiretroviral agents have an extraordinary number of drug interactions. The non-nucleoside reverse transcriptase inhibitors and the protease inhibitors are metabolised through the cytochrome P450 pathway, and the effects

of concomitant administration of protease inhibitors with other agents in the same class are discussed, as well as the effects of concomitant administration of protease inhibitors with non-nucleoside agents. The potential for numerous and medically risky drug interactions emphasises the importance of planning antiretroviral prophylaxis in consultation with practitioners or clinical pharmacists who are skilled in the use of these agents and knowledgeable about the potential for significant drug interactions that could either reduce the benefit of prophylaxis or increase the potential for toxicity.

Another common problem encountered by individuals managing postexposure prophylaxis programmes relates to the administration of chemoprophylaxis to a pregnant healthcare worker who has sustained an occupational exposure to HIV. We address what is known about the potential for toxicity and emphasise the recently published warning concerning the deaths of pregnant women and their offspring from lactic acidosis while receiving regimens containing stavudine and didanosine.

In April 1988, as a direct result of an occupational HIV infection that occurred in a technologist working in the Department of Transfusion Medicine in our hospital,[1] the Clinical Center of the National Institutes of Health began offering, as part of a nonblinded clinical trial, postexposure prophylaxis with zidovudine to healthcare workers who sustained occupational exposures to blood or body fluids from patients infected with HIV.[2,3] Staff members who sustained occupational HIV exposures and who elected to take zidovudine chemoprophylaxis were asked to sign an informed consent document that provided relevant information concerning the administration of zidovudine. Other institutions made similar decisions;[3] however, several authorities expressed concern about the potential for serious toxicity associated with administering these agents to healthy healthcare workers.[4-6] In the ensuing 12 years, substantial evidence (reviewed by Henderson[7-9]) has been accumulated suggesting – albeit indirectly – that antiretroviral agents are likely to be efficacious in preventing occupational infections when administered as postexposure prophylaxis. Although these drugs are clearly not 100% effective in preventing infection, available evidence suggests a substantial protective effect associated with the administration of the agents as postexposure prophylaxis. A synopsis of the evidence suggesting postexposure efficacy is summarised in table I.

Based on these kinds of data, the US Public Health Service published guidelines in 1990 that included consideration of the use of antiretroviral agents for postexposure chemoprophylaxis for occupational HIV exposures.[20] Subsequently, the US Centers for Disease Control and Prevention (CDC) issued guidelines that recommended the use of antiretroviral chemoprophylaxis for certain types of occupational exposures.[21,22] As a result of the issuance of these guidelines, most centres in the US now offer antiretroviral chemoprophylaxis for occupational HIV exposures. Other public health authorities have assumed similar postures.[23,24] In the ensuing 10 years since the first guidelines were published, we have accumulated substantial experience with the agents used for chemoprophylaxis.

Occupational exposures to HIV almost inevitably produce substantial anxiety in the exposed healthcare worker. Each exposed worker requires extensive (and often repetitive) counselling about the risks (i.e. to him- or herself and to significant others), about the postexposure treatment, and about the adverse effects of treatment. The likelihood of an individual healthcare worker adhering to a prophylaxis regimen depends on several variables, among them:

(i) the perceived seriousness of the exposure;

(ii) the efficacy of counselling of the exposed worker about the risks of infection, what is known about the efficacy of prophylaxis, and what is known

Table I. Brief synopsis of evidence suggesting efficacy of antiretrovirals administered as postexposure prophylaxis for occupational exposures to HIV

1. Studies have demonstrated the safety and efficacy of antiretrovirals administered as postexposure prophylaxis in animal models of retroviral infections[10-13]
2. Studies in humans have demonstrated antiretroviral efficacy in preventing vertical HIV transmission,[14] including some studies in which only the infants (and not the mothers) received treatment[15,16]
3. A retrospective case-control study found that taking zidovudine as postexposure prophylaxis was associated with an 80% reduction in the risk for occupational HIV infection[17]
4. A single case report demonstrated apparent efficacy of protracted postexposure treatment of a child who had received a transfusion of HIV-infected blood[18]
5. A single case report detected HIV RNA in the plasma of an occupationally exposed healthcare worker while receiving 3-drug prophylaxis; the worker remained uninfected and also produced an HIV-specific cellular immune response[19]

(and what the exposed worker should anticipate) about the adverse effects associated with antiretroviral chemoprophylaxis;
(iii) the specific regimen chosen for prophylaxis (i.e. 2 versus 3 drugs, the duration of therapy, as well as the specific agents selected); and
(iv) the quality of follow-up care, including the extent to which regimen-related adverse effects are treated and the practitioner's sensitivity to the need for dosage reduction and/or regimen modification.

The purpose of this manuscript is to review what has been learned about the safety and tolerability of antiretroviral agents when they are administered as postexposure chemoprophylaxis for occupational exposures to HIV.

1. Regimens

Although a number of antiretroviral agents have been used for postexposure prophylaxis, the largest experience to date is with zidovudine monotherapy. Subsequently, 2-drug regimens (e.g. zidovudine plus lamivudine) and 3-drug regimens (e.g. zidovudine, lamivudine plus indinavir) have been recommended for postexposure prophylaxis for certain types of exposures.[22] A variety of other regimens have been used, particularly in settings in which the source patient for the exposure has extensive antiretroviral experience. Prophylaxis regimens currently recommended by the US Public Health Service are summarised in table II.[22] The US Public Health Service guidelines are currently being revised and the new guidelines will probably offer more latitude in the selection of both primary and alternative agents for prophylaxis.

2. Common Adverse Effects and Drug Interactions

Administration of antiretroviral agents for any indication – including postexposure prophylaxis – is associated with substantial adverse effects.[25] By far, the largest experience with antiretroviral chemoprophylaxis has been with the use of nucleoside analogues, specifically zidovudine. As a class, when used for postexposure prophylaxis, the nucleoside analogues have been implicated as being associated with bone marrow suppression (anaemia, neutropenia), gastrointestinal disturbances (nausea, vomiting, diarrhoea and abdominal pain), headache, neuropathies, myalgia, lassitude, malaise and insomnia. Subjective adverse effects are extremely common among healthcare workers taking zidovudine for postexposure chemoprophylaxis (75% in our study). Although severe toxicities are more common when these agents are used for the long term therapy of HIV-infected individuals, a few instances of more severe toxicities associated with nucleoside analogue administration for postexposure prophylaxis have been reported, including cases of severe rash with hepatic dysfunction[26] and seizures.[27]

Administration of protease inhibitors as part of a postexposure prophylaxis regimen has been commonly associated with gastrointestinal disturbances (nausea, vomiting, diarrhoea, and abdominal pain), hyperglycaemia, hyperlipidaemia, headache, anorexia, altered taste and/or paraesthesias. One case of lipodystrophy associated with a prophylaxis regimen has been reported.[28] In addition, a few cases of nephrolithiasis have been reported in association with the administration of indinavir as part of the prophylaxis regimen.[29,30]

Table II. US Public Health Service recommendations for postexposure prophylaxis[22]

Regimen	Application	Drug
Basic	Occupational HIV exposures for which there is a recognised transmission risk (based on risk factors for occupational infection identified in the CDC's retrospective case-control study[17])	4 weeks (28 days) of both zidovudine 600 mg/day in divided doses (i.e. 300mg twice a day, 200mg 3 times a day, or 100mg every 4 hours) and lamivudine 150mg twice a day
Expanded	Occupational HIV exposures that pose an increased risk for transmission (e.g. larger volume of blood and/or higher virus titre in blood) [based on the presence of 2 or more of the risk factors identified in the case-control study[17]]	Basic regimen plus either indinavir 800mg every 8 hours or nelfinavir 750mg 3 times a day[a]

a Indinavir should be taken on an empty stomach (i.e. without food or with a light meal) and with increased fluid consumption (i.e. drinking 6 glasses of water throughout the day); nelfinavir should be taken with meals.

CDC = US Centers for Disease Control and Prevention.

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) have not been primary choices for prophylaxis in most published guidelines.[20-22] Nonetheless these drugs are being used in some settings as part of postexposure regimens. Rash occurs commonly with these agents and may sometimes be confused with the HIV seroconversion illness. Fever and gastrointestinal symptoms are common with the NNRTIs. Two cases of severe hepatic dysfunction (one requiring liver transplantation) have recently been reported in healthcare workers receiving nevirapine as part of a prophylaxis regimen.[31,32] In addition, 10 more cases of hepatic dysfunction have been reported in association with nevirapine-containing prophylaxis regimens. Finally, the US Food and Drug Administration (FDA) has received 2 reports of 'possible' Stevens-Johnson syndrome cases in healthcare workers taking nevirapine as a component of a prophylaxis regimen.

As a group, the antiretrovirals have a remarkable number of potential drug interactions. A complete accounting of all of the possible interactions is well beyond the scope of this manuscript. Nonetheless, certain of the interactions have substantial therapeutic implications; others may produce a dramatically increased potential for adverse effects.

For example, the nucleoside analogues all have additive adverse effects when administered together. Zidovudine and stavudine exhibit antagonism (and antagonism is also produced when zidovudine and ganciclovir or zidovudine and ribavirin are administered together). Administration of probenecid, fluconazole or valproic acid may significantly increase zidovudine concentrations. Because of the problem of bone marrow suppression, nucleoside analogues should be cautiously used with other agents known to suppress the marrow. Lamivudine concentrations are increased by cotrimoxazole (trimethoprim-sulfamethoxazole). Didanosine depends on an acidic environment for absorption, and hence should not be given with food or antacids. A potential exists for increased neuropathy when didanosine is used with other agents known to cause peripheral neuropathy (e.g. vinca alkaloids, isoniazid). Similarly, stavudine neurotoxicity can be potentiated by didanosine or zalcitabine.

Protease inhibitors also have numerous drug interactions. These drugs are metabolised by the cytochrome P450 (CYP450) pathway and administration of virtually all of the protease inhibitors depress drug metabolism by this pathway. Thus, concomitant use of 2 or more protease inhibitors results in increased concentrations of all of the agents. These agents should not be administered in combination with a whole variety of medications. Examples (by no means a comprehensive list) of agents that are contraindicated when using protease inhibitors include: quinidine, amiodarone, benzodiazepines, ergot alkaloids or rifampicin (rifampin). Simultaneous use of indinavir and rifabutin results in markedly increased concentrations of rifabutin. Conversely, consumption of nutritional supple-

ments, such as hypericum (St John's Wort), results in significantly lower serum concentrations of protease inhibitors. Grapefruit juice increases the concentration of saquinavir.

The NNRTIs are also metabolised through the CYP450 pathway and may either induce enzymes in this pathway or inhibit them. These interactions are quite complex. For example, simultaneous administration of efavirenz with a protease inhibitor may either increase or decrease blood concentrations of the protease inhibitor, depending on the protease inhibitor selected. For example, blood concentrations of indinavir, amprenavir and saquinavir are all decreased during concomitant use with efavirenz, whereas concentrations of nelfinavir and ritonavir are increased modestly when combined with efavirenz. If used with agents that are known to be metabolised via this pathway, drug concentrations should be monitored carefully. A major problem may be encountered when NNRTIs are used in combination with methadone in injection drug users, as the administration of nevirapine can precipitate the acute withdrawal syndrome.

All of the antiretrovirals should be administered with the close consultation of practitioners and/or clinical pharmacists who are knowledgeable about the drugs, their pharmacokinetics and their potential drug-drug and drug-food interactions.

3. Tolerability/Adherence

The experience (our own and the published information from the literature) with respect to tolerability/adherence to prophylaxis regimens is summarised in detail in tables III and IV. Our early experience with high dose zidovudine can be summarised as follows: approximately 51% of the healthcare workers offered the full 28-day course of zidovudine completed the therapy at the full dosage, and an additional 13% completed at a reduced dosage of zidovudine; thus, 64% of those initiating chemoprophylaxis completed the regimen.[33-37] The remaining 36% did not complete the course for a variety of reasons, including: grade 2 or higher symptoms (10%), unspecified subjective discomfort with taking antiretroviral prophylaxis (15%) and 'personal' reasons (10%) [e.g. family vacation, spousal advice, etc]. When this last group is excluded from the analysis, approximately 25% overall discontinued the agents at least in part because of adverse effects associated with the ther-

Table III. Toxicity associated with zidovudine monotherapy as postexposure prophylaxis (PEP)

Study characteristic	SFGH/NIH[33-39]	Italian Registry[40-45]	Forseter et al.[46]	CDC[47]	Schmitz et al.[48]
Number enrolled in PEP study	155	643	60	236	14
Participants reporting adverse effects (%)	75	49	73	75	64
PEP discontinued due to adverse effects (%)	25	20	30	31	43
Incidence of common adverse effects (%)					
nausea	58	38[a]	47	50	7
vomiting			10	11	
fatigue	70	12	30	33	50
headache	41	10	35	25	14
diarrhoea	10	8	5	8	
abdominal pain	20	12		8	
anorexia	22	3		5	
insomnia	28	3	8	3	
muscle aches	18	4	7	10	7
dizziness		3	3	3	

a Percentage is for nausea and vomiting combined.

CDC = US Centers for Disease Control and Prevention; **SFGH/NIH** = collaborative study conducted at the Warren G. Magnuson Clinical Center, National Institutes of Health and at San Francisco General Hospital.

Table IV. Toxicity associated with multidrug postexposure prophylaxis (PEP)

Study	Number in study	Drug regimen	Completion or adherence to therapy (%)	Toxicities reported
Sepkowitz et al.[49]	10	100% 3-drug (6 saquinavir, 4 indinavir)	30% did not complete course due to adverse effects	100% reported adverse effects No unexpected adverse effects reported
Swotinsky et al.[29]	68	33% 2-drug, 67% 3-drug	47% did not complete course due to adverse effects, 13% of patients receiving 3-drug PEP discontinued indinavir and completed course	75% reported adverse effects, Patients on 3-drug PEP reported more adverse effects. 1 patient developed nephrolithiasis. 1 patient developed severe pancytopenia
Fahrner et al.[50]	70	67% 2-drug, 33% 3-drug	35% did not complete course due to adverse effects	1 patient with elevated liver functions (on isoniazid), 1 patient developed acute hepatitis
CDC Needlestick Study[30]	43	35% 2-drug, 67% 3-drug	19% discontinued ≥1 drug due to adverse effects	77% reported adverse effects
NaSH[30]	287	56% 2-drug, 44% 3-drug	28% discontinued ≥1 drug due to adverse effects	46% reported adverse effects
CDC PEP Registry[30,51]	212	32% 2-drug, 68% 3-drug	29% discontinued ≥1 drug due to adverse effects	77% reported adverse effects
Italian Registry[30,52]	159	53% 2-drug, 47% 3-drug	13% discontinued ≥1 drug due to adverse effects	52% reported adverse effects
Gounden[30,52]	159	100% 2-drug	29% did not complete due to adverse effects	

CDC = US Centers for Disease Control and Prevention; **NaSH** = The National Surveillance System for Hospital health-care Workers.

apy. During this period we did not treat symptoms associated with administration of prophylaxis as aggressively as we do now. Had we done so, we suspect our completion rate may well have been significantly higher. Another factor contributing to the high rate of adverse effects in this study was the fact that we initially selected a high dosage of zidovudine (1200mg per day in 6 divided doses for the first 3 days, then 1000mg per day in 5 doses, skipping the 4am dose, for the next 28 days).

Interestingly, our experience with multiple drug prophylaxis is strikingly similar to the experience with high dose zidovudine.[50] Two-thirds of the exposed workers who were prescribed multiple drug prophylaxis regimens received 2 agents (primarily zidovudine plus lamivudine) and one-third received 3 drugs (with a protease inhibitor added as the third agent). Overall, 64% again completed the regimen, with slightly fewer completing the 3-drug regimen than those who took only 2 drugs. No serious toxicities were identified; however, symptoms were correlated with objective haematological and/or biochemical toxicities in 2 individuals (both of whom received the 3-drug regimen). Prophylaxis-related symptoms were again the primary reason that healthcare workers discontinued treatment. Others have reported similar findings with the 3-drug regimen.[29,49] Although we have an inadequate number of exposures to demonstrate statistical significance, since we have begun aggressively managing the symptoms associated with the chemoprophylaxis regimens and intensified our follow-up, we believe that the completion rate is increasing.

Finally, it is interesting to note that adherence may be increased if skilled counsellors provide advice to the drug recipients. In the San Francisco Post Exposure Prevention Project, the frequency of adverse effects was similar to those in the health-care worker studies; however, nearly 80% of participants completed the 4 weeks of therapy. The authors ascribed this success, in great measure, to

the intensive, skilled counselling that enrollees received.[53]

4. Duration of Prophylaxis

The duration of therapy is another factor that clearly affects adherence/tolerability. Intuitively, a shorter course is likely to be better tolerated, and some authorities have advocated using short courses of prophylaxis using higher dosages of antiretrovirals. Unfortunately, only limited information is available concerning the optimal duration for chemoprophylaxis. The most relevant information comes from animal models evaluating prophylaxis efficacy, as well as from studies evaluating the efficacy of antiretrovirals in preventing vertical transmission of HIV. Taken together, these data sources provide mixed results. In some of the animal models an extended course (i.e. 28 days) is essential to success. For example, Tsai et al.[10] evaluated the efficacy of the nucleotide analogue phosphonylmethoxypropyladenine in preventing simian immunodeficiency virus (SIV) infection in macaques. In this study, all of the macaques that were treated for 28 days were protected from SIV infection, whereas only half the animals that were treated for 10 days, and none of the animals treated for only 3 days following intravenous SIV infection, were protected from infection.[10]

Data from the vertical transmission studies have not directly addressed the question of duration of 'postexposure prophylaxis' for the newborn. However, in a study from Uganda, a single dose of nevirapine administered to the mother during labour combined with one dose administered to the newborn appeared to be superior to treatment with the course of zidovudine selected for the trial (i.e. in this trial, zidovudine was administered to the mother during labour and was also administered for 1 week to the infant).[54]

Because we think that these data do not definitively address the question of duration of postexposure prophylaxis, our current posture is to continue the 28-day course for postexposure prophylaxis, typically using the regimens outlined in table II.

5. Prophylaxis in Pregnancy

Administration of prophylaxis in pregnancy is associated with a different set of problems with respect to adherence/tolerability. Experience with antiretrovirals in pregnancy is quite limited, and we have sparse information about the pharmacokinetics of these agents in pregnancy and the potential for teratogenicity, carcinogenicity and/or mutagenicity of the agents in humans. A French study (comparing the efficacy of zidovudine alone versus zidovudine plus lamivudine in preventing vertical HIV transmission) identified a potential for life-threatening mitochondrial toxicity in the uninfected offspring of mothers taking these agents.[55] In this study, the investigators initially identified 2 infant deaths due to progressive neurological disease among those not infected with HIV. When their entire data set was analysed, an additional 6 cases of possible mitochondrial toxicity were identified. Thus, there was a total of 8 possible cases. Four of the mothers had received zidovudine alone and 4 received the zidovudine-lamivudine combination. As noted above, 2 cases were fatal. Of the additional 6 cases, 3 infants had substantial neurological findings (including one with status epilepticus, one with myopathy and seizures, and one with spastic diplegia and febrile seizures), and 3 were asymptomatic. All had elevated blood lactate levels. Both the FDA and the CDC have examined data sets looking for similar toxicity. The FDA has evaluated postmarketing data from the manufacturer of zidovudine and lamivudine and has not identified additional cases.[30] The CDC have examined data from several large cohort studies evaluating the efficacy of antiretrovirals in preventing vertical transmission without identifying additional deaths attributable to mitochondrial disease.[30] Nonetheless, in our view, the findings from the French study are troublesome and the reasons for the discrepancy in findings between the French and US studies are not clear. For these reasons we believe this issue should continue to receive additional scrutiny.

Early in 2001, the manufacturer of stavudine and didanosine issued a warning about the use of

this combination during pregnancy. The warning was based on the identification of 3 cases of fatal lactic acidosis in pregnant (or postpartum) women. The manufacturer cautions that the drug should be used only in instances in which the potential benefits clearly outweigh these and other risks of administration of these agents.[56]

A fairly substantial body of data is available about the use of zidovudine (and to a lesser extent, lamivudine) during pregnancy. Based on these data, and being mindful of the potential for mitochondrial toxicity noted above, both of these agents appear to be reasonably well tolerated for use in postexposure prophylaxis. Little is known about the safety of protease inhibitors during pregnancy. Certain adverse effects associated with their use (e.g. hyperbilirubinaemia and hyperglycaemia) may be highly relevant and particularly problematic during pregnancy.

Despite all of these cautions, pregnancy *per se* should not preclude offering postexposure prophylaxis to a pregnant healthcare worker who has sustained an occupational exposure to HIV. The responsibility of the clinician providing prophylaxis to counsel the exposed worker is redoubled in the setting of pregnancy. The pregnant worker should be counselled about the risks for HIV infection associated with her exposure, about what is known about vertical transmission (should she become infected), and about what is known about the potential risks and benefits to her and her offspring associated with administration of antiretroviral chemoprophylaxis. Although the available relevant data describing the use of postexposure prophylaxis during pregnancy are quite limited, we rely primarily on nucleoside analogues (i.e. zidovudine and lamivudine) in this setting. Others have elected to add a third agent (most often a protease inhibitor) to the regimen.

6. Discussion

Despite the apparent efficacy of antiretroviral agents administered as postexposure prophylaxis, several issues relevant to the safety and tolerability of these agents remain to be solved. As noted in section 3, combining the experience of several centres, nearly 75% of healthcare workers who took zidovudine as monotherapy for postexposure prophylaxis developed subjective symptoms associated with the treatment. Depending on the study, in 20 to 35% of these individuals the adverse effects were severe enough to cause discontinuation of the drugs. Similarly, small studies of the administration of 3-drug prophylaxis regimens have demonstrated adverse effects in 50 to 75% of those taking the drugs, with nearly 25% in each of 4 studies discontinuing treatment. In 3 studies conducted by the CDC, between 26 and 61% of individuals taking multiple drugs for postexposure prophylaxis failed to complete the prescribed regimen.[30]

To address these concerns, clinicians providing postexposure follow-up care should:

(i) frequently monitor individuals receiving treatment for treatable adverse effects;

(ii) be aware of the potential for drug interactions (discussed in more detail in section 2) that may occur among the antiretrovirals themselves, in addition to the interactions that are known to occur with certain benzodiazepines (e.g. midazolam, triazolam), antihistamines and oral contraceptives, as well as with other agents and dietary supplements;[57]

(iii) aggressively counsel the exposed worker at the time of initiation of therapy about the expected adverse effects and the strategies for managing those adverse effects, should they occur;

(iv) anticipate and, when appropriate, preemptively treat certain adverse effects (e.g. prescribe antimotility agents for anticipated diarrhoea associated with nucleoside analogues and protease inhibitors, or prescribe antiemetics for anticipated nausea); and

(v) reduce the dosage or modify the prophylaxis regimen if the healthcare worker cannot tolerate the course of therapy selected for prophylaxis.

Certain toxicities that have been identified in healthcare workers taking postexposure prophylaxis are quite troublesome. The 2 cases of severe hepatic decompensation associated with nevirapine-containing regimens will probably severely limit

its use in this setting. The problem of nephrolithiasis associated with indinavir administration, even though it can be precluded by adequate hydration (i.e. consuming 1.5L of fluid daily), makes other protease inhibitors somewhat more attractive for prophylaxis. The case of lipodystrophy associated with triple-drug prophylaxis,[28] the case of hepatotoxicity and rash associated with zalcitabine and zidovudine combination chemoprophylaxis,[26] and the occurrence of a case of zidovudine-associated seizures[27] are clear reminders of the seriousness of administering antiretroviral agents as postexposure chemoprophylaxis.

A major issue that needs to be addressed is the problem of overtreatment. Because postexposure therapy with antiretrovirals is far from benign, clinicians responsible for evaluating potentially exposed healthcare workers must be certain an exposure requiring intervention has occurred before prescribing antiretrovirals. Disturbingly, during both 1997 and 1998, 58% of the calls to the University of California at San Francisco's national postexposure prophylaxis 'hotline' were for instances in which the 'hotline' staff recommended either stopping or not starting postexposure prophylaxis.[7,58] We strongly advocate the development of a process by which those prescribing the postexposure regimen can have ready access to the advice of expert consultants who are knowledgeable about occupational exposures and about the use and toxicity of the agents being prescribed.

7. Conclusions

To assure the highest efficacy for a postexposure prophylaxis programme, we believe several guiding principles should be followed:

(i) treatment must be immediately accessible to all potentially exposed workers;

(ii) the clinician evaluating the potentially exposed worker must make certain that an exposure associated with a definable transmission risk has actually occurred;

(iii) the clinician should have ready access to, and should frequently use, the advice of expert consultants;

(iv) the clinician should choose a regimen that the worker will be able to take (i.e. some practitioners have assumed that 'if one drug is good, more will be better' and that assumption is clearly not valid in this setting);

(v) whenever the data are readily available, the clinician should be aware of the source patient's antiretroviral therapy and viral burden and should consider these data in tailoring a modified regimen that meets the specific needs of the circumstance of exposure (when appropriate);

(vi) the practitioner should counsel the exposed worker about known risks for transmission and the risks associated with treatment;

(vii) the practitioner should counsel the exposed worker about anticipated adverse effects and should pre-emptively prescribe symptomatic relief for the major anticipated adverse effects (e.g. nausea, vomiting, headache); and

(viii) the practitioner should schedule frequent (we advocate weekly) visits for follow-up and should carefully monitor for drug toxicity and for adherence while the healthcare worker is on the chemoprophylaxis regimen.

Taking this aggressive approach to the management of healthcare workers who elect to take postexposure antiretroviral chemoprophylaxis for occupational exposures to HIV may make it possible to increase the fraction of exposed workers who complete the regimen. We feel that it is imperative for each institution to maintain a staunch role of healthcare worker advocacy. Providing optimal care and follow-up for occupational exposures to blood-borne pathogens is one important mechanism through which an institution can express its advocacy for its workers.

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