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Review

The evolution of HIV treatment guidelines: Current state-of-the-art of ART

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ABSTRACT

Expert panels have provided guidelines for the treatment of HIV infection for more than a decade. The guidelines have evolved rapidly reflecting the remarkable improvements in HIV therapeutics over this time. From guidelines based mostly on expert opinion – the current guidelines are now primarily evidence-based recommendations – which the vast majority of treating clinicians accept and follow. We will highlight the major guideline recommendations for initiation of antiretroviral therapy – focusing on new data for the asymptomatic patient and those presenting with acute AIDS-related opportunistic infections. Given the number of new drugs available, we are currently able to offer virtually all patients in practice – a fully suppressive regimen, even in patients with substantial multi-drug resistant HIV. A remarkable achievement since AZT was first introduced for the treatment of HIV. This article forms part of a special issue of *Antiviral Research* marking the 25th anniversary of antiretroviral drug discovery and development, vol. 85, issue 1, 2010.

Contents

1. Introduction

For more than a decade now there have been guidelines for the treatment of HIV infection. Expert panels synthesize accumulating data from clinical trials and cohorts to provide treating clinicians ever-improving treatment recommendations. The guidelines have evolved over time from recommendations that were largely based on reasoned clinical expertise to guidelines that are now primarily based on evidence from well-conducted randomized controlled trials. Like the practice of HIV medicine, the treatment guidelines have evolved steadily over the past decade and are likely to continue to change with the advancement in antiretroviral therapies. In the beginning, guidelines often lagged behind clinical practice and were of little use to the front line practitioner. More recently, the guidelines are largely in line with clinical practice and are widely followed by practitioners.

In this article we will highlight the current state-of-the-art of antiretroviral treatment (ART) as reflected in the treatment guidelines with an emphasis on the most important new recommendations and data. This is not meant to be a comprehensive review of all of the studies that inform the guidelines – for that one is referred to the guidelines themselves. Although there are treatment guidelines from nearly every country where ART is available in this article we will focus on the guidelines from the IAS-USA panel, DHHS panel and recommendations from the CDC, NIH and HIV Medicine Association of the Infectious Diseases Society of

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America (Guidelines for the use of antiretroviral agents I HIV-1-infected adults and adolescents, 2008; Hammer et al., 2008; Kaplan et al., 2009).

2. When to start ART

Although the evidence for clinical benefit of ART for HIV-infected individuals is indisputable, staring ART in any given patient requires a careful weighing of the potential risks and the potential benefits of such treatment. It is clear that with suppression of HIV-replication most patients enjoy substantial benefits with improvements in immunologic status as reflected by increased CD4 counts, reduction of AIDS-related morbidity and mortality and in many cases a return to normal or near-normal quality of life (Palella et al., 1998; Detels et al., 1998).

The guidelines – from the earliest versions – have emphasized that any adult with symptomatic HIV infection (e.g. unexplained fevers, weight loss, diarrhea) should initiate ART as soon as possible as these patients are at increased risk for progression to AIDS-related complications. Similarly, patients with CD4 counts of <200 cells/μl have been recommended to start ART for more than a decade given data from clinical cohorts and clinical trials that consistently demonstrate reduction in AIDS-related morbidity and mortality.

Debate, however, continues as to the optimal timing for ART in asymptomatic adults with CD4 counts above 200 cells/μl. Current guidelines recommend ART when CD4 counts drop below 350 cells/μl but recent studies and improving treatment options have suggested to many experts that earlier starting times with CD4 counts up to 500 might be appropriate at least for some patients (The Strategies for Management of Antiretroviral Therapy (SMART) Study Group, 2006; Kitahata et al., 2009). The benefits of earlier ART seem to include not only a reduction in traditional AIDS-related complications but also reduction in cardiac, hepatic, renal diseases as well as non-AIDS defining cancers (The Strategies for Management of Antiretroviral Therapy (SMART) Study Group, 2006). The recently published NA-ACCORD cohort study, supports the earlier initiation of ART with a reduction in all-cause mortality when ART was initiated above 350 CD4 cells (Kitahata et al., 2009).

Guidelines also emphasize that earlier ART initiation should be considered in patients with co-morbid conditions and increased risks of disease progression. Of note, patients with high viral loads (i.e. >100,000 copies/ml), those with rapidly declining CD4 counts (i.e. >100 cells/year) and those patients co-infected with hepatitis B or C virus. More recently, consideration for non-AIDS-related risk factors have been emphasized – in particular increased cardiovascular risk factors might be an additional indication for earlier ART.

There is also a potential public health benefit to earlier ART in that studies have shown reduction in HIV transmission with lower viral loads or with ART in heterosexual couples (Quinn et al., 2003; Sullivan et al., 2009). In fact some experts have proposed widespread use of ART as a method of reducing HIV transmission on a global basis – the so-called "test and treat" strategy – although empirical evidence is still lacking. Mathematical models recently published suggest that a global program of universal voluntary annual HIV testing and immediate treatment for those who test positive no matter what their CD4 count is could dramatically reduce HIV incidence by reducing HIV transmission rates. The WHO model predicts that this strategy could end the worldwide pandemic within 50 years. Others have pointed out the numerous assumptions that underlie this model that will require further validation before this strategy could be implemented (Granich et al., 2009; Dieffenbach and Fauci, 2009).

Currently there is no definitive randomize clinical trial that makes clear the optimal timing of ART in asymptomatic adults with CD4 counts of 350 and above. The decision to start ART in this group of individuals comes down to one that is highly individualized for each patient and should include a discussion of patient readiness for what is – at this time still – a life long commitment to therapy.

3. When to start ART in setting of acute AIDS-related opportunistic infection (OI)

In 1987, AZT was shown in landmark studies to reduce clinical progression and death in patients with AIDS and thus ushering in the era of HIV treatment (Fischl et al., 1987). The benefit of antiretroviral therapy was substantially improved with the development of combination ART that included protease inhibitors. Since the mid-1990s, with the availability of protease inhibitors, the clinical benefits of ART have been clearly demonstrated in patients with advanced HIV-related immunodeficiency (i.e. CD4 <50 cells/μl) (Hammer et al., 1997; Hirsch et al., 1999; Cameron et al., 1998). Despite this knowledge and the unambiguous recommendations from the treatment guidelines to treat at earlier stages – many patients still enter into the healthcare system with late-stage HIV and/or AIDS diagnosis without the benefit of ART (Center of Disease Control and Prevention Website: http://www.cdc.gov; Giardi et al., 2007; Sabin et al., 2004; Schwarcz et al., 2006; Antiretroviral Therapy Cohort Collaboration, 2007).

Many of these "late-presenters" only come to medical attention when they develop an acute AIDS-related complication. A long-standing unanswered question had been the optimal time to initiate ART in the setting of acute AIDS-related OI. Specifically the issue is: "should ART be initiated at the time of the OI is being treated or should ART be deferred until the acute OI is treated?" Randomized controlled trials evaluating ART normally exclude patients with acute AIDS-related OI's so there was no data to clarify the optimal timing in this setting until recently.

The treatment guidelines now recommend that ART be initiated early during the course of the treatment of the OI as long as there is no compelling clinical contra-indication to doing so. In a recently published randomized phase IV strategy study conducted by the ACTG, AIDS-progression and death were reduced by 50% in patients receiving "early" ART, that is, ART given while treatment for the OI was ongoing compared to deferring ART until completion of the OI treatment (Zolopa et al., 2009). This reduction in clinical progression and death was associated with a more rapid increase in CD4 counts – which likely reduced the "window of vulnerability" to additional complications and/or death associated with advanced immunodeficiency. In a randomized controlled study of TB patients from South Africa, the introduction of ART while TB treatment was ongoing also showed a 50% reduction in mortality compared to waiting to start ART until after TB treatment was completed (Abdool et al., 2009). IRIS reactions and other adverse events were not seen to be increased with early introduction of ART in these studies and fear of IRIS should not be a reason to delay ART in these acutely ill patients.

4. What to start

In constructing an ART regimen for a patient the treating clinician now has some 25 different drugs in 6 different classes as well as a variety of fixed dose combination pills to choose from – a remarkable diversification in just 25 years since the introduction of AZT for the treatment of HIV! Despite the increasing diversity of drugs to choose from, the treatment guidelines have actually become more simplified and more straightforward as to the recommended choices for first line ART. Basically, a ritonavir-boosted

Table 1
DHHS guidelines modified by the author to include raltegravir as a new first line choice. One component from Column A and one component from Column B should be selected. Adapted from US Department of Health and Human Services Guidelines; revised November 3, 2008. Available at: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.

	Column A (NNRTI or PI or RAL)			Column B (Dual-NRTIs)
Preferred components	NNRTI EFV	PI ATV/r (QD), DRV/r (QD), FPV/r (BID), LPV/r (QD or BID)		TDF + FTC
		RAL	+	
Alternatives	NNRTI NVP	PI ATV FPV FPV/r (QD) SQV/r		ZDV + 3TC ABC + 3TC [if HLA-B*5701 negative] ddI + (FTC or 3TC)

PI with 2 NRTIs or a NNRTI with 2nRTIs is what is commonly recommended as preferred first line treatment for most HIV-infected adults (Table 1).

The actual choice of the specific regimen must include consideration for transmitted resistance (a baseline resistance test is now recommended for all patients who are about to start ART), pill burden, dosing schedule, tolerability profile, co-morbid conditions like cardio-vascular or renal disease and co-infections like hepatitis B and C, as well as, the anticipated long-term toxicity profile of the ART regimen. Given these considerations, most clinicians use the fixed dose combination that contains efavirenz (EFV), tenofovir (DF) and emtricitabine (FTC) as a convenient, well tolerated and effective single pill once-a-day regimen marketed as Atripla. However, as we can see from the table, one of several boosted PI regimens are recommended especially in the setting of transmitted NNRTI resistance, pregnancy, or other considerations. Several of the recommended boosted PIs can be dosed once a day along with daily fixed dose of TDF/FTC (marketed as Truvada).

For the first time in over a decade a new class drug – the integrase inhibitor raltegravir – has now been added to the preferred choices for first line ART to be used in combination TDF/FTC (Lennox et al., 2009). Although as of this writing the guidelines have not yet incorporated this choice – recent approval by the FDA as initial therapy will likely signal a change in guidelines – so that clinicians can choose between an NNRTI, a boosted PI or raltegravir – based regimen – all to be used in combination with the fixed dose combination of TDF/FTC.

The preferred nucleoside/nucleotide "backbone" for NNRTI, boosted PI regimens and raltegravir has been narrowed to a single choice – that of TDF/FTC because of toxicity concerns associated with the other choices. In particular thymidine analogs – zidovudine (AZT) and stavudine (D4T) are no longer part of the preferred list because of the increased risk of lipoatrophy and other metabolic complications associated with long-term use.

The guidelines also recommend against the use of unboosted PIs, or the use of "triple nuc" regimens (e.g. abacavir/lamivudine/zidovudine) because of lack of antiviral potency. In addition, dideoxyinosine (ddI) specifically combination with tenofovir as a nucleoside backbone is generally not recommended due to toxicity considerations.

5. When to change and what to change

Changes in ART are common and are normally done for virologic failure, adherence challenges or intolerance and toxicities. Although the choices are nearly endless given the number of drugs available again certain principles should be applied. At this moment given the number of new drugs available it is possible to provide a fully active ART regimen that will suppress HIV plasma viral loads to <50 copies in nearly every patient – even those with multi-drug resistant HIV. It is likely that this "golden moment" of HIV therapeutics will probably not last – we are already seeing a handful of patients developing integrase resistance and treatment failure in clinical practice – but it is a wonderful opportunity at this moment in time.

Single drug switches are not recommended and can only be done safely when the patient has achieved and maintained optimal viral suppression (i.e. plasma HIV viral load < 50 copies/ml) and is primarily done for toxicity or tolerability problems and needs to be monitored closely.

Generally, when a patient is on a failing ART regimen a resistance test is required to help guide the selection of a new regimen. Careful review of the patient's adherence patterns is also required to be sure that the new regimen meets the needs of the patient. In addition, the patient's entire ART treatment history needs to be reviewed along with any prior resistant tests so that the optimal regimen can be constructed in the setting of virologic failure. Generally speaking a new regimen needs to contain more than two active drugs but not more than three active drugs for the majority of patients to achieve a fully active regimen. A combination that includes partially active drugs is often required to round out the regimen and ensure long-term virologic success. The newer drugs that are available to construct regimens with two or three active drugs include new class drugs like the integrase inhibitor – raltegravir, CCR5 inhibitor – maraviroc, and new generation drugs like etravirine, darunavir, and tipranivir.

6. Special populations: pregnant women, children and adolescents

There are regularly updated guidelines for the treatment of HIV-infected children (Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, 2009). In general, the treatment recommendations parallel those for HIV-infected adults although there is more limited data available to base recommendations for treating children. In fact there are few randomized phase III trials of ART in children and results from adults trials are often extrapolated along with data from pediatric phase I/II safety and pharmacokinetic trials and non-randomized, open-label studies. For HIV-infected children younger than 3 years old neviripine is preferred and for those older than 3 years old, efavirenz with two NRTIs is recommended and for PI-based treatments, LPV/r with two NRTIs is preferred (DHHS Guidelines, 2008). Recommendations for adolescents are generally the same as those for adults.

In pregnancy the guidelines recommend the treatment of the infected mother independent of CD4 count in order to reduce the risk of vertical transmission but there are some special considerations for the specific drugs recommended in this setting. EFV is not recommended given it's potential for teratogenicity and AZT is still

recommended as a preferred NRTI given the accumulated clinical experience and proof of reduced vertical transmission as monotherapy (Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children, 2009).

7. Laboratory monitoring

The guidelines also provide recommendations for patient monitoring. Regular monitoring of CD4 count and plasma viral loads are recommended with the expectation that viral load will decrease by more than 1 log by 4 weeks and be <50 copies by 24 weeks given the potency of currently recommended regimens. CD4 counts may raise more slowly but in general should be monitored along with viral load measurements. Resistance testing–either genotype and or phenotype should be performed at baseline and generally results should be reviewed prior to initiating ART so as to tailor the regimen to the results. Resistance testing should also be performed in patients whose viral load rebound above 500–1000 copies after being suppressed or in patients who fail to achieve viral loads <50 copies/ml by 24 weeks. Tropism tests are available and required when considering a CCR5 inhibitor as part of the treatment regimen. HLA-B-5701 testing is also recommended prior to initiating abacavir as the risk for hypersensitivity reactions to abacavir is significantly higher in those patients who are positive for B-5701. Therapeutic drug monitoring (TDM) has not been proven to improve responses or limit toxicity. However, in special circumstances TDM may be helpful such as pregnancy, in children or in patients with renal or hepatic impairment.

8. Conclusions

The treatment pendulum for initiation of ART appears – as of this writing – to be swinging in the direction of earlier starts, that is before CD4 counts decline below 350. Unfortunately, most patients presenting with HIV infection are presenting "late" with CD4 counts below 200 and will not benefit from earlier ART. These patients should initiate ART as soon as possible. In patients presenting with acute AIDS-related opportunistic infections the evidence from recently completed clinical trials is clearly in favor of early initiation of ART, there is little justification for waiting until after the treatment of the acute OI is completed given the beneficial impact on clinical progression and mortality demonstrated in these studies. And finally, with the number of new drugs available to the clinician – both new generation and new class drugs nearly every patient in care today can be prescribed an ART regimen that is fully suppressive. The field of HIV therapeutics has witnessed tremendous progress since AZT was approved by the FDA in 1987 for the treatment of HIV infection and we can anticipate continued – but likely more incremental progress – in the near future.

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