J Antimicrob Chemother 2010; **65**: 1100–1107
doi:10.1093/jac/dkq096 Advance publication 25 March 2010

Journal of Antimicrobial Chemotherapy

Unmet therapeutic needs in the new era of combination antiretroviral therapy for HIV-1

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Significant advances in outcomes have been achieved with combination antiretroviral therapy (cART) in patients living with HIV. However, several ongoing needs remain with respect to the development of new treatments. The need for new or enhanced cART may become increasingly apparent as patients live longer with HIV and a greater proportion die from non-AIDS-related illnesses. Immunological response to cART is variable and immune failure occurs, despite virological control. Moreover, viral suppression can be incomplete due to insufficient antiviral efficacy, acquired or transmitted drug resistance, suboptimal pharmacokinetics/pharmacodynamics and lack of adherence. Chronic immune activation may continue even when viral replication is relatively restrained. Patients continue to experience cardiovascular and metabolic complications, due to disease, treatment and ageing. In addition, neurocognitive impairment and malignancy are important sources of ongoing morbidity despite cART. HIV also affects immune system senescence and bone turnover. This review discusses potential unmet needs with respect to these issues.

Keywords: HIV, persistence, co-morbidities, treatment, needs

Introduction

The hope expressed in the aftermath of the invention of the protease inhibitors that only 3 years of combination antiretroviral therapy (cART) would be curative[1] has turned out to be wishful thinking. Viral decay during cART occurs in phases, first primarily in productively infected CD4+ T cells with a half-life of 1–2 days. The second phase may reflect decay of HIV-infected macrophages and related cells or activation of latently infected cells with full-length unintegrated HIV DNA with a half-life of 2–3 weeks.[2] Finally, eradication of long-lasting or latently infected cells may require decades of suppressive therapy;[3,4] however, with the drugs currently available, eradication is unlikely to occur even with prolonged suppression.[5,6]

Many patients who achieve virological success (sustained plasma HIV-1 RNA < 50 copies/mL) continue to have very low-level viraemia that is detectable with a single RNA copy assay.[7] Residual viraemia may be due to periodic activation of extremely stable latently infected cells,[8] although other sources of low-level viraemia have been proposed.[9] Intensifying already 'successful' cART with raltegravir,[10,11] or with efavirenz, lopinavir/ritonavir or atazanavir/ritonavir[12] did not alter the residual viraemia, and there is no expectation that any of the current antiretroviral drugs will have a different effect.

Although cART has greatly reduced HIV-attributable morbidity and mortality,[13,14] ongoing issues include the aforementioned prolonged viral persistence, chronic immune activation, incomplete immune reconstitution and accelerated immune senescence. Moreover, as patients live longer, non-AIDS-related disorders are becoming more prominent, not only among those with modest immunological responses,[15] but also among those with higher CD4+ cell counts.[16]

Deficiencies of current cART

The primary goal of HIV treatment is to increase disease-free survival through maximal suppression of viral replication and preservation of immunological function;[17] however, this objective is not always achieved.

Immunological failure despite virological control

In patients who achieve viral suppression to <50 copies/mL within 1 year of initiating cART, the mean increase in CD4+ lymphocytes is ~175 cells/mm^3,[18] but the degree of this response is highly variable.[19] Overall, ~5%–27% of patients have no increase or only a relatively modest increase in CD4+ cells.[20–22] Incomplete viral suppression,[23] older age,[19,24] co-infection with hepatitis C[25] and delayed initiation of treatment[19] are some of the variables that consistently predict a poor immunological response. A poor CD4+ cell response increases the risk of AIDS-defining illnesses, non-AIDS-defining illnesses (such as cardiovascular disease and malignancy) and death,[23,26–29] although other investigators have reported more favourable outcomes.[30,31]

Of the currently available antiretroviral agents, ritonavir-boosted protease inhibitors (PIs)[32] and the chemokine receptor 5 (CCR5) antagonist, maraviroc,[33] appear to generate greater gains in CD4+ lymphocytes than does efavirenz in randomized controlled studies, although the clinical relevance of the difference is unproven. The combination of ritonavir-boosted PIs and CCR5 receptor antagonists may produce even greater CD4+ count increases in treatment-naïve individuals than currently approved combinations, although this also has not been demonstrated clinically.

To date, attempts to improve CD4+ cell counts and clinical outcomes using interventions other than antiretroviral drugs have met with only partial success, with no demonstrable clinical benefit. The most extensively studied agent, interleukin-2 (IL-2), did not improve survival or reduce mortality despite a quantitative CD4+ cell count increase.[34] This may be due to as yet uncharacterized functional defects in the CD4+ cells induced by IL-2 or negative effects of IL-2 that may neutralize any benefit on host defence.[34,35]

Interestingly, compared with patients with robust CD4+ cell increases after starting cART, poor immune responders have increased markers of immune activation. One hypothesis links this to ongoing microbial translocation based on evidence of increased circulating lipopolysaccharide (LPS; a marker of bacterial translocation) and corresponding detection of enterobacteria genome sequences in the plasma of some poor immune responders.[36,37] It is also possible that an association exists between microbial translocation and residual viraemia as patients with fully suppressed viraemia, defined as HIV-1 RNA <2.5 copies/mL, were found to have LPS levels that were similar to levels seen in uninfected persons whereas those with an HIV-1 RNA level between 2.5 and 50 copies/mL had higher LPS levels.[38] Interestingly, a correlation between microbial translocation and disease progression was not found in a study from Uganda.[39] If microbial translocation is confirmed to be important in the pathogenesis of HIV, at least in some settings, then it would be critical to explore whether differences exist in how specific antiretroviral agents and cART regimens may alter the interaction of HIV infection with gut microbiota and whether there is an impact on immune activation and immune restoration. Perhaps if antiretrovirals differ in their ability to preserve or restore gut immune function, the agents with greatest potency in this regard may be particularly relevant in acute or early infection, although it is unclear whether even very early cART can diminish the immunovirological damage that occurs during this phase.[40]

Incomplete viral suppression

The proportion of patients who achieve plasma HIV-1 RNA levels <50 copies/mL after 48 weeks of initial cART has increased over time,[41,42] even with salvage therapy—a week 48 suppression rate of ~90% was recently reported with the combination of darunavir, raltegravir and etravirine.[43]

Suboptimal adherence is a relatively common reason for virological failure and this is currently addressed in multiple ways, especially by the preference for once-daily well-tolerated regimens.[44] However, use of twice-daily regimens is still common in patients who have failed first-line therapy as a result of poor adherence. The expectation that a patient who adheres poorly to a well-tolerated once-daily regimen would achieve better adherence with twice-daily treatment may be impractical; thus, a need exists for additional once-daily second-line regimens. Potential once-daily novel combinations in PI-naïve patients or those with limited PI resistance include ritonavir-boosted PIs plus integrase inhibitors, although pharmacokinetic and efficacy studies are needed particularly since raltegravir, the only FDA-approved integrase inhibitor at present, is dosed twice daily.

Other reasons for virological failure include poor antiviral efficacy, acquired or transmitted drug resistance and suboptimal pharmacokinetics/pharmacodynamics. In addition, some agents have efficacy against a limited viral subset. For example, the CCR5 antagonists lack activity against CXCR4- and dual/mixed-tropic strains. Likewise, the investigational maturation inhibitor, bevirimat, lacks significant activity against viral isolates that contain the relatively common bevirimat resistance-associated polymorphisms in the HIV *gag* gene.[45] An investigational algorithm predicted responders and non-responders with 80% and 89% accuracy, respectively.[46]

Immune activation

When exposed to antigenic stimulus, the normal immune system mounts an appropriate response and then returns to relative quiescence after clearing the antigen. HIV disrupts this balance by provoking chronic immune activation, cytokine elaboration and ultimately alteration of the microenvironment of the immune system.[47] The immune activation set point during acute HIV infection as measured by the level of CD8+ T cell activation correlates with the pace of subsequent CD4+ cell decay in untreated patients.[48] Immune activation has also been proposed as a potential explanation for the low CD4+ cell count (<350 cells/mm^3) present in up to 10% of elite controllers.[49,50] In addition, immune activation can continue in some patients receiving virally suppressive cART.[31] In a recent study, levels of immune activation markers in blood remained elevated even after 6 years of antiretroviral therapy and were associated with lower CD4+ cell counts.[51]

Despite the apparent central role of chronic immune activation in HIV pathogenesis, most prospective randomized studies of different cART regimens have focused on virological outcome, CD4+ cell increase and safety. However, a fourth component, 'immune quieting', is rarely assessed. Overall, the immune pathogenesis rationale seems sound and may tip the balance toward one particular regimen if there are several with similar antiviral efficacy, convenience and tolerability.

Cardiovascular and metabolic complications

HIV-associated cardiovascular disease risk appears to be reduced by virologically suppressive cART regardless of the regimen.[52] A similar improvement in brachial artery flow-mediated dilatation (FMD)—a marker of endothelial function—was demonstrated with lopinavir/ritonavir plus two nucleos(t)ide reverse transcriptase inhibitors (NRTIs); efavirenz plus two NRTIs; or lopinavir/ritonavir plus efavirenz.[52] Furthermore, viral load changes in that study were strongly associated with FMD, suggesting that the crucial factor in improving endothelial function was control of viraemia and not the specific antiretroviral regimen used.[52]

However, cART itself can contribute to cardiovascular disease risk through several mechanisms, such as induction or worsening of dyslipidaemia, which can be substantial with some ritonavir-boosted PIs, but less so with others, such as atazanavir.[53] Other potential adverse effects of some cART include increased risk of metabolic syndrome including dysglycaemia, endothelial dysfunction[54] and coronary artery calcification.[55]

After correcting for established cardiovascular risk factors (except dyslipidaemia) in the D:A:D. study, the incidence of myocardial infarction was 1.53 per 1000 person-years in those not exposed to PIs compared with 6.01 per 1000 person-years in those exposed to PIs for >6 years.[56] The degree of risk increased with each year of additional PI exposure. The effect of PI use in the D:A:D. study was reduced but not eliminated by controlling for dyslipidaemia. To date the D:A:D. study has evaluated predominantly older PIs; the study has not yet accumulated enough data on newer PIs, such as atazanavir and darunavir/ritonavir, which may have more favourable metabolic profiles. Differences in the cardiovascular risk profile among PIs[51,53,56] are not fully explained by the effects on lipids.[56] Importantly, increased myocardial infarction risk was not seen with non-nucleoside reverse transcriptase inhibitors (NNRTIs).[56] Nevirapine was recently found to be associated with greater increases in high-density lipoprotein (HDL) and a better lipid profile overall compared with atazanavir/ritonavir.[57] Thymidine analogues can also increase triglycerides, total cholesterol and low-density lipoprotein levels. In addition, abacavir and didanosine have been associated with increased risk of cardiovascular disease in some studies.[58] However, the association of abacavir with cardiovascular events is controversial, particularly when adjustments are made for chronic kidney disease, which is itself an independent predictor of cardiovascular disease.[59,60] Recent cohort studies that have singled out lopinavir/ritonavir,[61–63] fosamprenavir[63] and indinavir[62] as being associated with cardiovascular events underscore the need for more research in this area.

The mechanisms by which antiretroviral agents are linked to adverse cardiovascular risk outcomes are not definitely known, but hypotheses have been put forward for some of the classes. For example, the effects of PIs on serum lipids appear to be mediated by the partial homology of HIV-1 protease to regions in two adipocyte regulatory proteins, which causes PIs to bind to these proteins and inhibit lipid metabolism.[64] Abnormal endothelial function was observed in abacavir-treated patients in one study.[65] Improved understanding of the mechanisms of cardiovascular disease from HIV and/or antiretroviral therapy and determination of the cART regimens with the lowest cardiovascular risk are urgent research priorities.

Neurocognitive impairment

Neurocognitive impairment is an important source of ongoing morbidity in HIV-infected individuals taking cART. HIV itself has been implicated in this process, but co-morbidities such as substance abuse, depression, hepatitis C virus (HCV), vitamin B_{12} deficiency, thyroid dysfunction and neurosyphilis are potential confounders. Viral replication and neurological pathology that manifest as encephalopathy, encephalitis, dementia or CNS lymphoma can occur in patients with undetectable plasma virus presumably because the CNS functions as a separate compartment and sanctuary site.[66,67] In one study of 200 patients who had maintained viral load <50 copies/mL for a median of 48 months and had no current intravenous drug use or major depression, 27% had cognitive complaints and 84% of those patients had manifestation(s) of HIV-associated neurocognitive disorder (HAND) including mild neurocognitive impairment in 52% and dementia in 8%. Asymptomatic neurocognitive impairment was detected in 60% of those who offered no cognitive complaints.[68] Antiretroviral drugs vary in their ability to penetrate into the CSF which is used as a surrogate for CNS penetration,[69] and agents with the best penetration appear to be the most likely to suppress viral replication in the CSF and perhaps in the CNS. However, this characteristic has not always been shown to correlate with improved cognition.[70] Some PIs, such as saquinavir,[71] have limited CNS penetration, but this is not necessarily a class effect since darunavir generally achieves CSF concentrations that exceed the median inhibitory concentration for wild-type virus.[72]

Malignancies

Proposed mechanisms for the development of cancer in HIV-infected patients include impaired immune surveillance, chronic B cell stimulation, genomic instability, role of oncogenic viruses and dysregulation of cytokine and growth factor production.[73] Current cART regimens partially correct these pathways and while there has been a decrease in the incidence of some AIDS-defining malignancies (non-Hodgkin's lymphoma and Kaposi's sarcoma),[74–76] non-AIDS malignancies such as Hodgkin's lymphoma and cancer of the oropharynx, anus, lung and skin have assumed increased importance. Some of these malignancies are more common in HIV-infected persons receiving cART compared with HIV-seronegative individuals, and may not be associated with CD4+ cell count or nadir CD4+ cell count.[77,78] However, current CD4+ cell count is generally predictive of the risk for AIDS- and non-AIDS-associated malignancies except anal cancer, which may be better predicted by duration of immunodeficiency.[79] The severity of immune suppression as measured by CD4+ T cell count is predictive of mortality from AIDS- and non-AIDS-associated malignancies,[80,81] and it has been suggested that cART would be most beneficial if it restores or maintains CD4+ cell counts at levels >500 cells/mm^3.[79] Emerging data on non-AIDS-associated malignancies probably reflect opposing risks to some extent. As AIDS death rates fall, the proportion of deaths due to other causes such as non-AIDS-associated malignancies will increase, even if there is no 'true' increase in overall risk. No confirmed associations between any of the currently approved antiretroviral drugs and malignancies have been observed.

Ageing

HIV appears to accelerate immune senescence since persistent replication may lead to clonal exhaustion of HIV-specific immune cells which, with other systemic effects, may culminate in premature ageing of lymphocyte populations and impaired renewal in a manner similar to natural ageing.[82,83] It is possible that HIV hastens end-organ associations of ageing as well. Increased vascular ageing (measured by coronary artery calcium) was observed in 41% of 400 HIV-infected patients in

a recent cross-sectional study.[84] Accelerated ageing is one the least elucidated potential associations of HIV infection in terms of magnitude, clinical implications and role of cART. Research in this area has gained importance with the ageing of the HIV-infected population.

Effects on bone

HIV infection is also associated with decreased bone mineral density (BMD), osteopenia and osteoporosis. Some antiretroviral drugs may also contribute to this problem.[85,86] In the SMART substudy, uninterrupted cART was associated with greater decline in BMD,[87] but there was no consistent association with any antiretroviral drug or class. Other investigators also found no difference in bone loss between lopinavir/ritonavir- or efavirenz-containing cART.[88] However, understanding of the interaction between specific antiretroviral drugs and bone loss is evolving. Tenofovir was associated with decreased BMD in early studies[89] and this may be linked to renal phosphate wasting.[90,91] Efavirenz also induces cytochrome P450 enzymes and may accelerate the metabolism of active vitamin D to inactive metabolites.[92] Vitamin D deficiency appears to be common in HIV-infected patients; it was reported to be present in 91% in a cohort from London,[93] while the prevalence reported in 55 ambulatory HIV-infected persons from Boston was 36.8% moderate and 10.5% severe deficiency.[94] Overall, a phenotype characterized by frailty similar to that associated with ageing can occur in HIV-infected patients.[95] Optimally, antiretroviral therapy should aim to interrupt and reverse bone disorders in HIV-infected persons.

The ideal antiretroviral therapy

An increasing number of cART regimens can suppress HIV replication and increase CD4+ cell counts, but each differs with respect to side effect profiles, rates of adherence and metabolic consequences. The ideal cART for each patient should accommodate a variety of host and viral factors, especially pre-existing illness and known or suspected viral resistance, in order to maximize the benefit of therapy.

All currently recommended first-line regimens include two NRTIs, but this class of antiretroviral drugs is not necessary to achieve viral suppression. An NRTI-sparing regimen of lopinavir/ritonavir plus efavirenz has similar virological efficacy to efavirenz plus two NRTIs.[32] Although the combination of lopinavir/ritonavir and efavirenz is relatively unattractive because of increased risk of dyslipidaemia and NNRTI resistance, other potential two-drug regimens warrant further research. Darunavir may be a particularly attractive component of two-drug cART because it is associated with one of the highest instantaneous inhibitory potentials (log reduction in single round viral infectivity at clinically relevant concentrations).[5] Maraviroc has gained interest because it is associated with a greater CD4+ cell count increase[33] and an earlier decline in immune activation when compared with other agents.[96] It is also associated with increases in CD8+ cells.[97] Unravelling whether any of these effects have clinical implications will be useful for defining the role for maraviroc and other CCR5 inhibitors. Integrase inhibitors, such as raltegravir, rapidly suppress plasma HIV RNA.[98] The clinical significance of this observation also needs to be established.

Selected drugs in development

Much emphasis has been placed on finding compounds that can overcome resistance to older agents and be administered once daily. The integrase inhibitor class includes elvitegravir, which is administered once daily but must be given with a pharmacological enhancer such as ritonavir or possibly the investigational agent GS 9350.[99] Elvitegravir, however, exhibits cross-resistance with raltegravir. The most recent integrase inhibitor to enter clinical development (S/GSK1349572) has generated enthusiasm based on preclinical and early clinical studies. Monotherapy with a once-daily 50 mg dose produced a 2.5 $\log_{10}$ reduction in viral load, and by day 11, 9 of 10 patients receiving the drug achieved a viral load <400 copies/mL, and 7 of 10 achieved a viral load <50 copies/mL.[100] In contrast to raltegravir, S/GSK1349572 has limited intersubject pharmacokinetic variability.[101] Preliminary data also suggest that this drug has a higher barrier to resistance *in vitro* than raltegravir or elvitegravir and appears to retain activity *in vitro* against many raltegravir-resistant variants.[100,102,103] However, these preliminary findings need verification in larger trials, and activity against resistant variants will need to be tested clinically.

In the NNRTIs class, rilpivirine appears to have similar virological efficacy and may have fewer CNS side effects compared with efavirenz.[104] RDEA427 and RDEA640 are in pre-clinical trials and appear to have *in vitro* activity against efavirenz-resistant variants,[105] findings similar to those described for UK453,061 (lersivirine) and IDX 899.[106,107] These latter agents have also shown anti-HIV activity in proof of principle studies in individuals with NNRTI-sensitive virus.[106,107] Vicriviroc, another CCR5 antagonist, has a long half-life that allows once-daily dosing and can be boosted by CYP3A4 inhibitors. Although efficacy in treatment-experienced patients was seen in a Phase II trial (VICTOR-E1),[108,109] Phase III studies (VICTOR-E3 and 4) failed to demonstrate superiority of vicriviroc over placebo in patients receiving a potent background regimen.[110] In treatment-naïve patients, increased virological failure occurred with vicriviroc compared with efavirenz in one study, perhaps due to suboptimal dosing of vicriviroc.[111]

Other agents in development include PRO 140, a subcutaneously administered humanized monoclonal antibody that blocks HIV binding to CCR5. The 5 or 10 mg/kg dose of PRO 140 resulted in an average viral load drop of 2 logs, and the effect was durable for several weeks.[112]

It is not yet known whether any of these agents in development will fill current gaps in HIV treatment strategies. As new agents advance into clinical use, a strong emphasis must be placed on identifying those with the best long-term tolerability given the emerging consensus that early initiation of continuous cART is desirable.[113,114] Along these lines, pharmacoenhancers that are free of ritonavir-related metabolic effects will enrich the treatment armamentarium.

Conclusions

HIV treatment is in an era when suppression of plasma virus to levels <50 copies/mL is achievable for most infected patients. The challenge for clinicians and researchers now is to avoid complacency with the current treatment paradigm. Opportunities remain to optimize immune restoration, viral suppression and

clinical outcomes, and also to mitigate chronic immune activation and its adverse consequences.

Transparency declarations

B. T. has received research support from Pfizer and Tibotec, and served on the advisory board of both companies. C. H. has received research support from Bristol-Myers Squibb, Pfizer, Merck, GlaxoSmithKline, Tibotec and Gilead, and serves on advisory boards for Bristol-Myers Squibb, Merck, GlaxoSmithKline, Tibotec and Gilead. J. E. has been an investigator for Merck, Panacos, GlaxoSmithKline, Taimed and Abbott on research grants to the University of North Carolina, has served as a paid consultant or speaker for Merck, Abbott Diagnostics, Avexa, Inhibitex, Bristol-Myers Squibb, GlaxoSmithKline, Gilead, Tibotec, Roche and Pfizer, and has been a consultant to Trimeris in the past.

Assistance with manuscript preparation, funded by Schering Corp., a Division of Merck & Co., was provided by Sui Generis Health (New York, NY, USA). The authors received no financial compensation.

Author contributions

B. T. wrote the first draft of the manuscript, which was reviewed and edited by C. H. and J. E.

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