HAART has increased the life expectancy of HIV-infected individuals significantly. Optimal adherence to HAART results in viral suppression and immune recovery in the majority of HIV-infected persons. Data from the early HAART era suggest that adherence levels of greater than 95% are necessary to achieve and maintain virological suppression. However, the optimal threshold of adherence required to maximize the pharmacological benefits of contemporary antiretroviral regimens, particularly in the virologically suppressed patient, is unknown. This review examines new data on the role of adherence in the late HAART era, focusing on virological, immunological and epidemiological aspects. We begin with a discussion of the impact of adherence on viral dynamics and immunological parameters in the virologically suppressed patient. We then review the importance of adherence in emerging antiretroviral treatment strategies. Finally, we summarize accumulating data on the role of antiretroviral adherence in the prevention of HIV transmission. Taken together, the data reviewed reinforce the critical importance of adherence in the management of HIV infection in the late HAART era.

Introduction

HAART has increased the life expectancy of HIV-infected individuals significantly [1]. Uninterrupted access and optimal adherence to HAART result in viral suppression and immune recovery in the majority of HIV-infected persons [2]. Observational and cohort data suggest that adherence levels of greater than 95% are required in order to achieve and maintain virological suppression and avoid the emergence of drug resistance mutations [3,4]. However, much of the data on optimal thresholds of adherence are based on studies performed in the early HAART era, prior to the advent of boosted protease inhibitor (PI) regimens, the availability of coformulated pills and daily dosing of first-line therapy, and the widespread use of ultrasensitive viral load assays.

In the late HAART era, generally defined as the year 2000 to the present, HIV-infected individuals with access to first- and second-line regimens are likely to achieve and maintain virological suppression. In an analysis of viral load trends in a closed cohort, Ledergerber et al. [5] found a significant increase in the proportion of subjects achieving virological suppression over time, from 38% in 2000 to 70% in 2008. Recent data also show that adherence levels necessary to maintain virological suppression vary with time. Rosenblum et al. [6] demonstrate that adherence requirements diminish over longer durations of virological control. Thus, an individual who remains virologically suppressed for a period of 12 months has a lower risk of virological failure than a patient suppressed for less than 6 months, even at adherence levels between 50 and 75% [6]. Lima et al. [7] have similarly shown a decreasing risk of viral rebound with increasing time on suppressive HAART, independent of adherence levels.

It has been widely documented that different HAART regimens have distinct levels of ‘forgiveness’ to various adherence patterns [8,9]. In general, boosted-PI-based regimens remain robust even in intermittently adherent patients, while non-nucleoside reverse transcriptase inhibitor (NNRTI)-based combinations require stricter adherence but may allow for scheduled breaks such as ‘weekend drug holidays’ [10,11]. New strategies in antiretroviral management are emerging, introducing additional variables into clinical practice. Nevertheless, full adherence to daily dosing remains standard of care for all antiretroviral regimens.

Virological suppression is considered by many clinicians to be a proxy for perfect adherence. However,
high rates of non-adherence to both ritonavir-boosted PI (PI/r)- and NNRTI-based regimens have been observed in virologically suppressed patients [12,13]. The nuanced nature of emerging data on adherence demands an in-depth assessment of the complex behavioural patterns contributing to adherence in clinical practice, even in the virologically suppressed patient.

The interrelationship between regimen potency, reduced toxicities, dosing convenience and duration of virological suppression raises new questions about the optimal threshold of adherence required to achieve maximal benefit from HAART. In this review, we examine new data on the role and importance of adherence in the late-HAART era. We begin with a discussion of the relationship between adherence, viral dynamics and immunological parameters in the virologically suppressed patient. We then review the impact of adherence on emerging antiretroviral strategies. Finally, we present accumulating data on the role of antiretroviral adherence in the prevention of sexual HIV transmission. We believe that these data reinforce the critical importance of adherence in the management of HIV infection in the late HAART era.

Virological and immunological aspects

Viral reservoirs

Persistent, low-grade viral replication has been observed in patients on long-term, virologically suppressive HAART. Furthermore, HIV RNA can be detected in non-plasma compartments in a small but significant portion of patients on long-term suppressive treatment. These compartmentalized sites, in which antiretroviral drug penetration may be diminished, include cerebrospinal fluid (CSF), semen and cervicovaginal secretions [14]. Ongoing viral replication in these non-plasma reservoirs may have both clinical and epidemiological implications, as discussed below.

Eden et al. [15] measured HIV RNA viral load in the CSF of 69 neurologically asymptomatic, virologically suppressed subjects receiving HAART for at least 6 months. Detectable HIV RNA viral load was observed in the CSF of 10% of aviraemic subjects. Detection of HIV RNA in the CSF was associated with a higher number of previous viral ‘blips’ (defined as an isolated HIV RNA measurement >50 copies/ml) and with more frequent treatment interruptions (defined as episodes of antiretroviral therapy [ART] abstinence >2 weeks associated with a viral rebound). In a study of antiretroviral concentrations in the central nervous system (CNS), Letendre et al. [16] show an association between lower adherence to HAART and higher levels of CSF viral load.

In light of the continued risk of HIV-associated neurocognitive disorders in the late HAART era, ongoing viral replication in the CNS has been advanced as a potential causal explanation and target for pharmacological intervention. Canestri et al. [17] report on a small group of subjects with unexplained neurocognitive impairment despite undetectable plasma viral load while on HAART. In all subjects, detectable viral replication was noted in the CSF. Improvements in both neurocognitive symptoms and suppression of CSF viral replication were observed after optimization of antiretroviral regimens based on increased CNS penetration effectiveness score or genotypic susceptibility of the CSF viral strains [17]. Although it is clear that adherence to HAART leads to parallel reductions in both plasma and CSF viral loads, it is not entirely clear why some patients fail to achieve an undetectable viral load in the CSF despite a persistently undetectable plasma viral load [18]. The relationship between degree of HAART adherence and CSF viral load in the virologically suppressed patient has not been clearly delineated and is likely a complex one. Recent data suggests that defects in executive function are associated with poorer adherence, and vice versa [19].

Multiple studies have demonstrated the presence of HIV RNA in the semen and cervicovaginal fluids of patients on suppressive HAART. In a longitudinal study, Cu-Uvin et al. [20] measured genital tract viral load in 59 virologically suppressed women on HAART. Paired plasma and genital specimens were obtained at nearly 600 study visits. Over the course of the study, 37% of women had a discordant detectable genital tract viral load while plasma viral load remained undetectable. Graham et al. [21] measured genital HIV shedding in 102 women initiating first-line ART in Kenya. Lower adherence was the key variable associated with persistent vaginal and cervical HIV shedding, and remained statistically significant after adjustment for plasma HIV RNA viral load [21].

Amongst men on suppressive HAART, the genital tract has been shown to represent a distinct viral reservoir site and the proportion of men with detectable HIV RNA in semen has been reported to be between 3% and 15% [22]. Barroso et al. [23] conducted a prospective study of 93 men initiating antiretroviral therapy. Self-reported adherence to ART was highly associated with seminal HIV RNA suppression at 6 months of therapy. However, most men received dual nucleoside therapy and few achieved an undetectable plasma viral load at 6 months.

The persistence of HIV RNA in the genital tracts of virologically suppressed patients raises concern about the potential for ongoing sexual transmission amongst aviraemic patients on HAART. The evidence cited above suggests that adherence may be important in suppressing compartmentalized genital tract viraemia independently of its effect on plasma viral inhibition.
However, the precise threshold of adherence required to control HIV replication in viral reservoirs remains unknown.

Control of copathogens

Immune recovery and virological suppression have been associated with accelerated eradication of copathogens. The immune protective role of virological suppression \emph{per se}, independently of CD4+ T-cell recovery, is also associated with reduced rates of opportunistic infections. An undetectable viral load has recently been incorporated into the DHHS guidelines algorithm for discontinuation of primary and secondary opportunistic infection prophylaxis [24].

Adherence to HAART has been associated with increased clearance of viral copathogens. Minkoff \emph{et al.} [25] examined the relationship between adherence and the incidence of human papilloma virus (HPV) infection and low-grade squamous intraepithelial lesions in women receiving HAART. Good adherence by self-report, defined as >95% of doses taken on at least two consecutive visits, was associated with a 50% reduction in the risk of incident oncogenic HPV infection over the course of the study. In addition, a fourfold higher odds of spontaneous squamous intraepithelial lesion clearance was noted in adherent versus non-adherent subjects [25]. In a case-control study of cervical dysplasia in 180 HIV-positive women, adherence to HAART was associated with a significantly higher rate of lesion regression [26].

Data on the impact of adherence to HAART on other virally mediated diseases (for example, HPV-associated anal cancer, hepatitis C related end stage liver disease) and non-infectious comorbidities (for example, cardiovascular disease), beyond the established benefits conferred by viral suppression and immunological recovery, remain under investigation.

Areas of uncertainty: residual viraemia, immune recovery and activation

As stated above, the virological and immunological benefits of maintaining an HIV RNA viral load below the current level of detection of <50 copies/ml is well established. Adherence is the major predictive factor associated with achieving and maintaining an undetectable viral load [27,28]. Since the early HAART era, the ability to detect HIV RNA has improved significantly, with ultrasensitive assays commercially available in most resource-rich settings. In clinical practice, commercial assays available in the US and Europe can detect viral loads as low as 20 copies/ml [29]. In trial settings, assays with a level of detection as low as a single RNA copy are frequently used. The sensitivity of these assays raises complex questions about the extent to which viral replication must be suppressed. The prognostic relevance of \emph{residual viraemia}, generally defined as a viral load of <50 copies/ml in patients receiving HAART, has been investigated, with conflicting results.

Geretti \emph{et al.} [30] analysed the prognostic value of residual viraemia on the risk of subsequent virological failure. An increased risk of virological failure was observed in subjects with higher levels of residual viral load. Mavinger \emph{et al.} [31] analysed the relationship between residual viraemia and immunological recovery in a case-control study of 23 patients on suppressive HAART. A statistically significant relationship was noted between the absence of residual viraemia and immune recovery, defined as an increase of >500 CD4+ T-cells/ml [31]. In contrast, Havlir \emph{et al.} [32] found no relationship between CD4+ T-cell gains or subsequent virological rebound in virologically suppressed subjects with residual viraemia, defined as a viral load of >2.5 but <50 copies/ml.

Low-level viral replication has been shown to contribute to persistent immune activation, a process linked to qualitative deficits in T-cell function [33]. In a study of 32 virologically suppressed patients, Ostrowski \emph{et al.} [34] found an association between residual viraemia, defined as detectable viraemia of <20 HIV RNA copies/ml, and immune activation markers such as soluble tumour necrosis factor 2 and beta 2 microglobulin.

The complex relationship between residual viraemia, inflammation, immune activation and immune recovery is of uncertain clinical significance at this juncture. Furthermore, no data has been published demonstrating a relationship of stricter adherence to the presence of residual viraemia. Of note, intensification strategies, wherein a new antiretroviral drug is added to a fully suppressive HAART regimen, have demonstrated conflicting results in terms of residual viral load [35,36]. More study is required in order to elucidate the relationship of adherence levels to risk of residual viraemia, inflammation and immune activation in the virologically suppressed patient.

Alternative antiretroviral strategies

Despite the relative simplicity, efficacy and safety of contemporary HAART regimens, significant problems persist in current treatment strategies. Such problems encompass, but are not limited to, long-term toxicities, side effects, the emergence of viral resistance and cost [37]. Standard antiretroviral therapy generally involves the use of three agents from two different drug classes [24]. New antiretroviral strategies seek to simplify this approach while maintaining its virological potency. The following is a discussion of new treatment strategies and the relationship of adherence to their efficacy.
Protease inhibitor maintenance monotherapy

PI/r-based induction and maintenance approaches are the most investigated of emerging antiretroviral strategies. ‘Induction’, with a standard HAART regimen of three drugs from two classes is used in order to achieve virological suppression. The induction phase is followed by ‘maintenance’ with a single PI/r. Inclusion criteria in most induction/maintenance trials require subjects to have an undetectable HIV RNA viral load for 6 to 12 months at baseline, thus selecting for a study population with relatively high levels of adherence. The rationales for monotherapeutic maintenance regimens include decreased pill burden, reduced long-term toxicities, improved quality of life and lower costs [38]. PI/r monotherapeutic regimens are more frequently used in Europe, while at present US guidelines recommend that PI/r monotherapy be used in the context of a clinical trial [24].

The OK04 study was an open label, randomized, non-inferiority trial comparing lopinavir/r maintenance monotherapy versus lopinavir/r plus two nucleoside reverse transcriptase inhibitors (NRTIs) therapy in virologically suppressed patients. At 96 weeks, the PI/r maintenance monotherapy arm was found to be non-inferior with respect to rates of virological failure [39]. Poor adherence, assessed with a standardized six question self-report tool, was significantly associated with virological failure in a subgroup analysis of the monotherapy arm [40].

In the MONOI trial, darunavir/r maintenance monotherapy was compared to darunavir/r plus two NRTIs in virologically suppressed patients. This study failed to prove the non-inferiority of the maintenance monotherapy approach, with more episodes of intermittent low grade viraemia and a higher proportion of treatment failures in subjects with a baseline HIV RNA >100,000 copies/ml in the monotherapy arm [41]. Adherence levels did not differ between study arms. Subjects who always reported 100% adherence were less likely to have a virological failure than those reporting lower rates of adherence. The authors conclude that adherence may be ‘more crucial’ in monotherapeutic strategies. The MONET study, however, a similar trial of darunavir/r maintenance monotherapy, demonstrated non-inferiority of the monotherapy arm despite stricter virological outcomes. Episodes of low-grade viraemia in either arm were associated with poorer adherence [42].

In addition to concerns that induction/maintenance regimens may be less efficacious than standard HAART [38], questions remain regarding the ability of monotherapy to suppress viral replication in non-plasma compartments. In induction/maintenance studies using lopinavir/r or atazanavir/r, HIV RNA was detected in the CSF and genital secretions in a portion of participating subjects [43,44]. The previously described relationship (see Virological and immunological aspects) between adherence to traditional antiretroviral regimens, plasma viral suppression and compartmentalized viral replication has not been determined for PI/r monotherapeutic regimens.

PI/r-based monotherapeutic regimens provide hypothetical benefits in terms of adherence by reducing pill burden, side effects and long-term toxicities. However, stricter adherence may be required to achieve equivalent rates of virological suppression. A thorough adherence assessment is crucial in identifying appropriate candidates for induction/maintenance approaches.

Nucleoside reverse transcriptase inhibitor sparing regimens

A number of NRTI-sparing strategies have also been investigated in clinical trials. This approach, which generally substitutes the use of NRTIs with an agent from another class, reduces toxicities and conserves future treatment options. Riddler et al. [45] conducted a randomized three arm trial comparing efavirenz plus two NRTIs, lopinavir/r plus two NRTIs, and efavirenz plus lopinavir/r in 757 treatment-naive subjects. The NRTI-sparing arm was equal in virological efficacy to the efavirenz-based triple therapy arm, but showed higher metabolic toxicities. No differences were noted in rates of adherence between the arms. Whether NRTI-sparing regimens provide benefits, or require more stringency, in terms of adherence is under investigation in a number of studies on alternative antiretroviral strategies [46,47].

Regimen simplification

Regimen simplification, defined as the reduction in pill burden with no or minimal pharmacological alteration, has been shown to increase adherence and quality of life. In a study by Airoldi et al. [48] more than 200 virologically suppressed patients were switched from a three- or two-pill regimen of efavirenz plus tenofovir plus lamivudine or emtricitabine to a one pill fixed-dose combination regimen of efavirenz/tenofovir/emtricitabine. The original and simplified regimens were pharmacologically identical. Reduction in pill burden was associated with significant increases in perceived quality of life and adherence.

Epidemiological aspects

Insights into the relationship between HIV viral load and infectiousness have led to a paradigmatic shift in the use of antiretroviral treatment for the purpose of HIV prevention [49]. Some of the most notable advances in HIV prevention in recent years incorporate the use of antiretroviral agents.
Pre-exposure prophylaxis

Pre-exposure prophylaxis (PrEP) refers to the use of antiretroviral agents in HIV-negative individuals at risk of HIV infection. Results of two randomized controlled trials evaluating the use of ART in PrEP were published in the past year. The CAPRISA 004 trial evaluated a tenofovir-containing vaginal gel in the prevention of HIV transmission to high-risk heterosexual women [50]. The study showed a significant reduction in HIV transmission in the treatment arm, with an overall efficacy of 39%. As such, the results of CAPRISA 004 represent the first successful use of a vaginal gel in the history of HIV prevention research. However, in a prespecified subgroup analysis, only those women reporting treatment adherence levels of greater than 80% had a statistically significant reduction in HIV acquisition. In this adherent subgroup, the effectiveness of the gel in reducing HIV transmission was 54%.

The results of the first randomized trial of systemic ART in the prevention of HIV transmission showed similar promise. The Pre-Exposure Prophylaxis Initiative (iPrEx) study randomized high-risk men who have sex with men and transgender women to a PreP strategy of daily oral tenofovir/emtricitabine versus placebo [51]. A 44% reduction in the risk of HIV transmission was observed in the treatment arm. A post hoc subgroup analysis showed a significant relationship between adherence and risk reduction. The hazard ratio for HIV infection in subjects who took more than 90% of doses was 0.27, a 73% reduction in risk. There was no statistically significant reduction in the risk of HIV acquisition amongst subjects reporting less than 90% adherence.

Based on these data, the use of topical and/or systemic pre-exposure ART in HIV-uninfected individuals is likely to expand substantially over the next few years. PrEP raises new questions about ART adherence in a population that has not been extensively studied, namely HIV-uninfected individuals. Data on adherence amongst HIV-uninfected persons receiving ART for the purpose of post exposure prophylaxis after sexual exposure suggest very low levels of adherence in this context [52,53]. It is unclear whether post exposure prophylaxis data is generalizable to HIV-uninfected persons reporting treatment adherence levels of greater than 80% had a statistically significant reduction in HIV acquisition. Only those women reporting adherence levels of greater than 80% had a statistically significant reduction in HIV acquisition. In this adherent subgroup, the effectiveness of the gel in reducing HIV transmission was 54%.

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HAART in the epidemiological control of sexual transmission

Maintenance of an undetectable plasma HIV viral load has been associated with significant reductions in sexual transmission amongst discordant heterosexual couples [54]. In an observational study of 3,381 HIV-discordant heterosexual couples, antiretroviral treatment was associated with a 92% reduction in the risk of HIV transmission [55]. The sole transmission event in the treatment group occurred in a patient who had not yet achieved virological suppression. Although adherence levels were not measured, viral suppression was observed in 70% of subjects at 7 months, suggesting moderately-high levels of adherence.

Most recently, a randomized trial of the efficacy of HAART in reducing sexual transmission amongst 1,763 serodiscordant couples was terminated prematurely due to a significant reduction in new infections in the early treatment group [56]. The trial demonstrated a 96% reduction in vireomically-linked transmissions amongst couples randomized to immediate versus deferred antiretroviral treatment. Adherence levels were high in both arms, with 79% and 74% of subjects reporting >95% antiretroviral adherence in the early and delayed arms, respectively. The role of adherence to HAART in the prevention of sexual transmission will undoubtedly assume a critical place as widespread treatment prevention strategies, such as a ‘test and treat’, are implemented [57].

Conclusions

New data on the virological, immunological, clinical and epidemiological uses of antiretroviral agents raise novel questions about the role of adherence in the late HAART era. We believe that the sum of the evidence reviewed provides a compelling argument for a renewed emphasis on adherence. Even as regimens become simpler and more potent, multiple compelling rationales argue for strict adherence to contemporary HAART- and ART-based prevention regimens. In Table 1, we summarize the rationales for an invigorated focus on adherence to contemporary antiretroviral regimens. Many adherence interventions, including physician- and patient-administered assessments, have shown to be clinically efficacious and cost-effective [58,59].

Suboptimal adherence to HAART puts the patient at risk of viral rebound and immunological failure, even once virological suppression has been attained. Moreover, viral escape in non-plasma compartments is widely documented, with potential clinical and epidemiological implications. Both treatable and untreatable comorbidities may indirectly benefit from high adherence levels in the virologically suppressed patient. The data on prevention and epidemiological control provides the most definitive data to date on the need for ongoing high levels of adherence.

Adherence is a complex behavioural and systemic process [60]. Enabling the patient to achieve and maintain high adherence levels is the responsibility of the clinician. An adherence assessment, followed...
Antiretroviral adherence should be assessed in every clinical encounter. Patient self-reported adherence assessments are a simple, validated and cost-effective tool.

Suboptimal adherence patterns are also observed in virologically suppressed patients on HAART, therefore, an undetectable viral load should not be used as a proxy for adherence assessment.

Suboptimal adherence has been associated with persistent viral reservoirs in the central nervous system and genital compartments, even in virologically suppressed patients on HAART.

Adherence to HAART has been associated with more rapid clearance of some viral copathogens, such as human papilloma virus. The benefits of strict adherence on the control of other infectious and non-infectious comorbidities in the virologically suppressed patient is unclear.

The impact of adherence on residual viraemia, immune activation and immune recovery, beyond that conferred by viral suppression, is as yet undetermined.

Novel antiretroviral strategies, such as mono- and dual antiretroviral drug regimens, may require stricter adherence thresholds in order to identify optimal candidates and ensure safe follow-up.

Antiretroviral therapy has been proven to greatly reduce the rates of HIV transmission amongst heterosexual couples. The optimal threshold of adherence remains to be defined.

Adherence is a key determining factor in the efficacy of antiretroviral-based pre-exposure prophylaxis of sexual HIV transmission.

by interventions to improve and support adherence, should be employed in all clinical encounters. Since virological suppression is expected and achieved by most patients on HAART, new data should be incorporated into patient–physician discussions and adherence support programmes. As our understanding of HIV pathogenesis and transmission deepens, we continue to believe in the essential benefits that HIV-infected patients, and their partners, derive from complete adherence.

Disclosure statement

The authors declare no competing interests.

References


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