New strategies to optimize treatment for HIV-1 infection

Polyana Monteiro d'Albuquerque

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Cover ilustration: reproducció del grafit de Keith Haring, 1958 - 1990, *Todos juntos podemos parar el sida*, que l'artista nord-americà va executar l'any 1989 a la plaça de Salvador Seguí de Barcelona.

El 1992 es va enderrocar l'edifici que el sustentava, afectat pel Pla especial de reforma interior del barri del Raval. L'Ajuntament de Barcelona i el Museu d'Art Contemporani de Barcelona - MACBA - n'han fet aquesta reproducció en 2014, en el marc del Raval Cultural.

Col.lecció MACBA.
Fons de l'Ajuntament de Barcelona.

Fotography: Alexandre Bahia Vanderlei

Polyana Monteiro d'Albuquerque was born in Recife, Brazil on 1977. Obtained the medical degree at the Federal University of Pernambuco, Recife in 2001. She went on internal medicine residency program at *Hospital Barão de Lucena* (2002-2004) and later on infectious disease residency program at *Hospital Oswaldo Cruz* (2004-2007), Recife. Since then she has been working at *Hospital Oswaldo Cruz* and *Hospital Correia Picanço* as an infectious diseases specialist. In 2010 she obtained a master degree in Tropical Medicine at Federal University of Pernambuco, Recife, and started a fellowship in HIV at the Infectious Disease Unit, Hospital Clínic, University of Barcelona, under supervision of Prof. Esteban Martínez. Until the present date, she has worked as an associated investigator at the AIDS research group, Hospital Clínic, University of Barcelona, where she developed the research work for this thesis.

Universitat de Barcelona

New strategies to optimize treatment for HIV-1 infection

Tesi presentada per Polyana Monteiro d'Albuquerque
Per obtenir el títol de doctor a per la Universitat de Barcelona
Dirigida per Esteban Martínez Chamorro

Programa de doctorat Medicina - Universitat de Barcelona - 2015

HUB Health Universitat de Barcelona Campus

B:KC Barcelona Knowledge Campus
Campus d'Excel·lència Internacional

À minha mãe.

FREVO Nº 1 DO RECIFE,
Antônio Maria (1951)

Ô Ô saudade

Saudade tão grande

Saudade que eu sinto

Do Clube das Pás, do Vassouras

Passistas traçando tesouras

Das ruas repletas de lá

Batidas de bombos são maracatus retardados

Chegam da cidade cansados

Com seus estandartes no ar

Que adianta se o Recife está longe

E a saudade é tão grande

Que eu até me embaraço

Parece que eu vejo Walfrido Cebola no passo

Haroldo, Mathias, Colaço

Recife está dentro de mim

"PASSO DO FREVO", Recife
Pierre Verger (1947)

Contents

Antiretroviral terminology

ART - Antiretroviral therapy

ARV - Antiretroviral (drug)

EI - Entry Inhibitors

FI - Fusion Inhibitors

HAART - Highly active antiretroviral therapy

INSTI - Integrase strand-transfer inhibitor

NNRTI - Nonnucleoside reverse transcriptase inhibitor

NRTI - Nucleoside (nucleotide) reverse transcriptase inhibitor

PI - Protease inhibitor

PIMT - Ritonavir-boosted protease inhibitor monotherapy

STR - Single-tablet regimen

Antiretroviral drugs

3TC - Lamivudine

ABC - Abacavir

ATV -Atazanavir

ddI - Didanosine

DRV - Darunavir

d4T - Stavudine

EFV - Efavirenz

ENF - Enfuvirtide

ETR - Etravirine

EVG - Elvitegravir

Abbreviations

FTC - Emtricitabine

IDV - Indinavir

LPV/r - Lopinavir/ritonavir

NVP - Nevirapine

RAL - Raltegravir

RPV - Rilpivirine

RTV - Ritonavir, (used as booster=/r)

TAF - Tenofovir alafenamide fumarate

TDF - Tenofovir disoproxil fumarate

ZDV - Zdovudine

COBI - Cobicistat

Other Abbreviations

HIV-1 - Human immunodeficiency virus type-1

CYP3A4 - Cytochrome P450 3A4 enzyme

CHD - Coronary heart disease

CVD - Cardiovascular disease

HDL-c - High-density lipoprotein cholesterol

LDL-c - Low-density lipoprotein cholesterol

MI - myocardial infarction

TC - Total cholesterol

TG - Triglycerides

VL - Viral load (HIV-RNA)

“Sem um fim social, o saber será a maior das futilidades”.
Gilberto Freyre

Introduction

BACKGROUND

ROLE OF TREATMENT FOR HIV-1 INFECTION

Nucleoside reverse transcriptase inhibitors - NRTIs

Nonnucleoside reverse transcriptase inhibitors - NNRTIs

Protease inhibitors - PIs

Integrase strand transfer inhibitor - INSTIs

HIV-1 INFECTION, ANTIRETROVIRAL THERAPY, AND COMORBIDITIES

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BRIEF OUTLINE OF THE THESIS

BACKGROUND

The AIDS pandemic began more than 30 years ago and has killed up to 40 million people. Despite the fact that 35 million people are living with HIV worldwide, the response to AIDS epidemic have faced undeniable progress over the past 10 to 15 years. The number of people who are newly infected with HIV-1 is decreasing and more people are now receiving antiretroviral therapy (ART). In addition, fewer people are dying of AIDS-related diseases (Figure 1). Since 2005, when the highest number of deaths was reported, AIDS-related deaths has declined by 35%.[1]

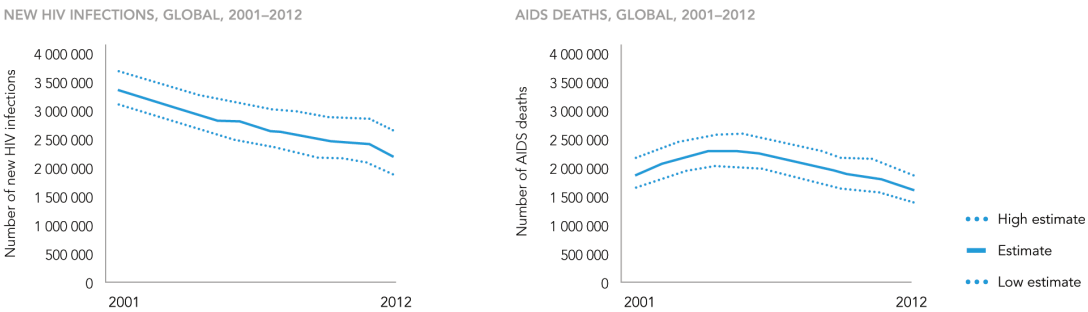

Figure 1. Numbers of new HIV infections, and AIDS deaths, 2001-2012, globally. Source: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Gap_report_en.pdf.

While AIDS defining events have been steadily decreasing as a cause of death, the proportion of deaths attributed to non-AIDS related conditions, such as cardiovascular disease, cancers, and end-stage liver and renal disease, has increased over the past years [2, 3, 4] and life expectancy of HIV-1-infected patients is still lower than that in the general population of a similar age. [5, 6, 7] The reasons for this excess mortality are not yet fully understood. Probably, it is partly a result of increased life expectancy with widespread use of combination ART, but also because HIV-1 infection is related to several chronic conditions (Figure 2). [8, 9, 10]

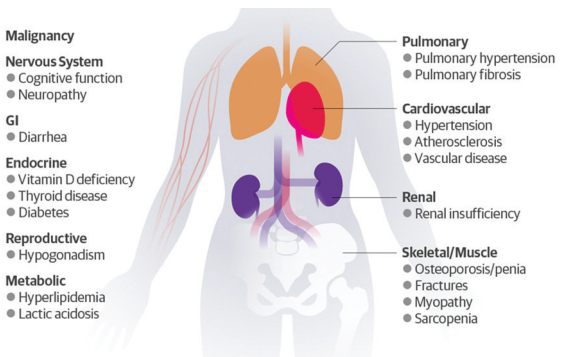

Figure 2. Range of non-AIDS chronic conditions that can complicate the care of people living with HIV. Adapted from a presentation given by Professor Wafaa El-Sadr of Columbia University and ICAP, at a meeting on strengthening services for chronic diseases and HIV, held in Ethiopia in 2010.

Effects of uncontrolled viral replication leading to immune activation, inflammation, coagulation, and lipoprotein particle changes is thought to contribute to higher rates of cardiovascular and other end-organ damage reported in HIV-1-infected cohorts. HIV-1 replication and activation of lymphocytes and monocytes is associated with release of inflammatory cytokines and early vessel dysfunction. [11, 12, 13] Similarly, past or present HIV-1-induced immune depression reflected by the CD4 cell nadir or the CD4/CD8 cell ratio were identified as risk factors for noninfectious comorbidities. [8, 14] Suppression of HIV-1 replication with ART attenuate, though incompletely, some of these mechanisms, but exposure to ART is also associated with variable toxicity that may increase risk of comorbidities. [15] Underlying lifestyle factors, including smoking and alcohol use, often common among HIV-1-infected individuals, may also play a part in this discrepancy in life expectancy (Figure 3). [16, 17]

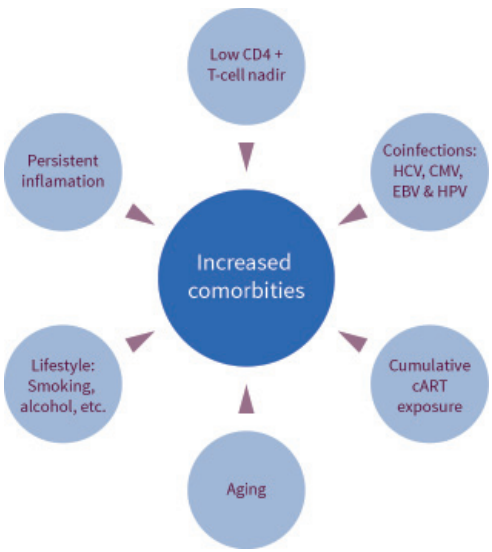

Figure 3. Factors that are thought to be implicated in the pathogenesis of non-AIDS related conditions. Adapted from Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med. 2011;62:141-55.

ROLE OF TREATMENT FOR HIV-1 INFECTION

At present, eradication of HIV-1 infection cannot be achieved with available regimens and treatment for HIV-1 is considered lifelong. ART consists of a combination of drugs targeting the HIV-1 life cycle with the aim of stopping HIV-1 replication. The primary goals of ART for the treatment of HIV-1 infection are to reduce the disease progression preventing HIV-1-associated morbidity and mortality, to restore and preserve immunologic function and to prevent HIV-1 transmission. [18]

There are 6 available classes of antiretroviral (ARV) drugs targeting several steps of HIV life cycle. The fusion inhibitor, enfuvirtide (ENF), and the CCR5 coreceptor antagonist, maraviroc, block fusion and viral binding, respectively, at virus entry. The nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) act at reverse transcription, in which the single stranded HIV-1 RNA is transcribed into double-stranded DNA by the HIV enzyme reverse transcriptase. Integrase strand transfer inhibitors (INSTIs) target the integration of HIV DNA into the DNA of the host cell. The site of action of protease inhibitors (PIs) is the cleavage of the transcribed proteins into smaller components (Figure 4).

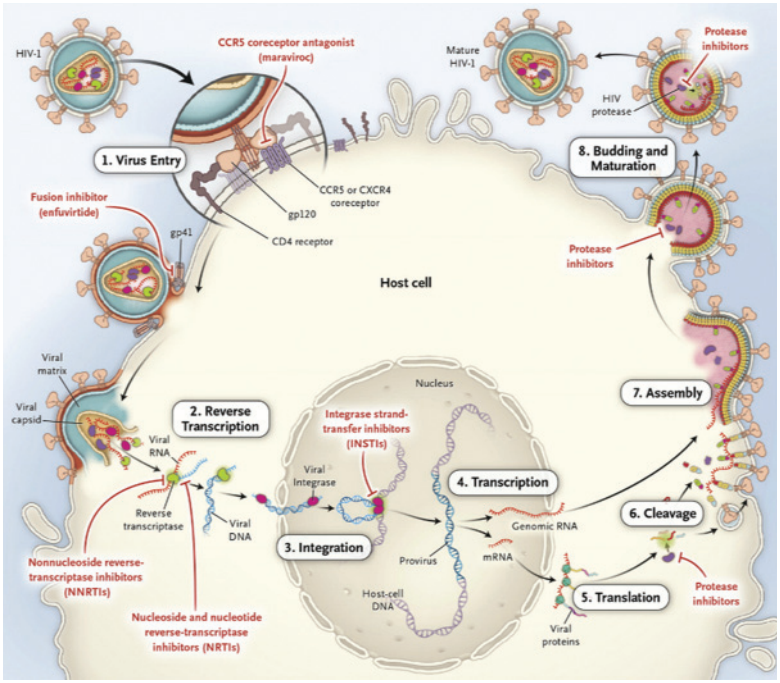

Figure 4. Reproductive cycle of Human Immunodeficiency Virus type 1 (HIV-1) and sites of action of the major classes of antiretroviral medications. Source: Gandhi M, Gandhi RT. Single-pill combination regimens for treatment of HIV-1 infection. N Engl J Med. 2014 Jul 17;371(3):248-59.

Because of the high replication and mutation rates of HIV-1, multiple ARV agents must be taken simultaneously to suppress replication and prevent the development of viral resistance. After 1996, it became clear that combining three active drugs from two or more drug classes, known as HAART (highly active antiretroviral therapy), could result in sustained suppression of viral replication and increase in CD4+ cell count. [19, 20] Since then, combination ART has dramatically reduced HIV-1-associated morbidity and mortality and has transformed HIV-1 disease into a chronic, manageable condition. [21, 22, 23, 24] Figures 5 illustrate the decline in the number of AIDS deaths during the first 10 years of the HAART era.

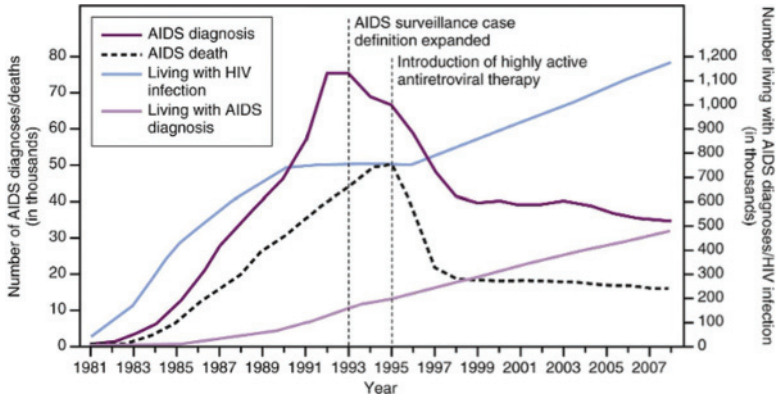

Figure 5. Acquired immunodeficiency syndrome (AIDS) cases, deaths, and persons living with acquired AIDS by year, 1981 to 2008, United States. Source: Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8ª ed. Philadelphia: Elsevier-Saunders; 2015. 1489 p.

The Joint United Nations Programme on HIV/AIDS in its annual update reported that the number of people receiving ART worldwide has tripled over the last five years. As of June 2014, 13.6 million people, 38% of all adults living with HIV, had access to ART. [25] In June 2013 the World Health Organization (WHO) updated its treatment guideline, written primarily for use in resource-limited settings, and recommended starting treatment when CD4 count is less than 500 cells/μL. Accordingly to this CD4 threshold for treatment initiation, WHO estimates that the number of people in need of ART will increase up to 30.7 million in 2015. [26]

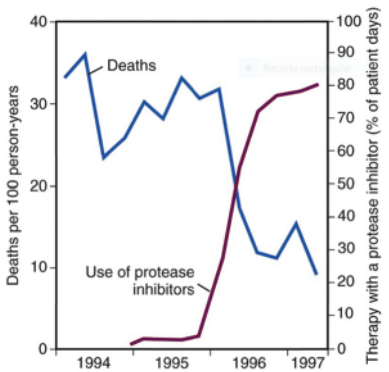

Figure 6. Incidence of death and use of protease inhibitors in HIV-1-infected patients with a CD4+ count lower than 100/mm3 in the HIV Outpatient Study. Source: Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8ª ed. Philadelphia: Elsevier-Saunders; 2015. 1546 p.

At present, with use of available ARV, nearly all adherent HIV-1-infected patients are able to achieve sustained virologic suppression.[27] Maximal and sustained viral suppression is the foundation for immune recovery, it decreases inflammation and immune activation and preserves CD4 T-cell numbers. Additionally, it prevents the selection of drug-resistance mutations and reduces the spread of HIV at a community level.[28, 29, 30, 31]

The body of evidence supporting earlier initiation of ART indicates that HIV-1-infected patients should start treatment earlier in order to achieve substantial clinical and prevention benefits, improving survival and reducing the incidence of HIV-1 infection. [30] We can speculate that at some point every person infected with HIV-1 will eventually need treatment. Indeed, the US Department of Health and Human Services (DHHS), and the International Antiviral Society–USA, have updated their treatment guidelines in 2014 and recommend ART for all HIV-1-positive patients regardless of CD4 count. [18, 32] Recommendations for the initiation of therapy are developed and updated by an international panel of experts in HIV-1 research and patient care, based on data from randomized clinical trials in ARV-naive patients. For the overwhelming majority of patients, initial regimen consists in a combination of 2 NRTIs and a third active agent, either an INSTI, a NNRTI, or a protease inhibitors boosted with ritonavir (PI/r). [18, 32, 33, 34]

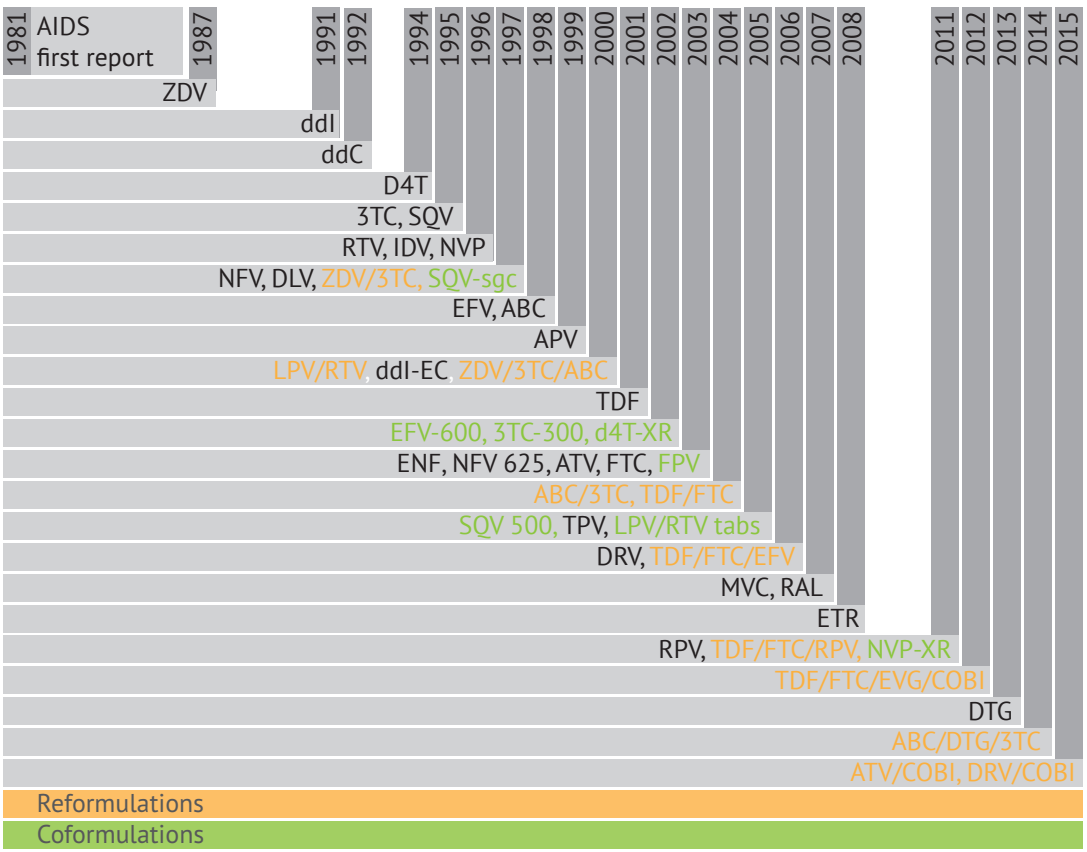

Figure 7. Timeline for development of antiretroviral agents. Dates indicate FDA approval. 3TC, lamivudine; ABC, abacavir; APV, amprenavir; ATV, atazanavir; COBI, cobicistat; d4T, stavudine; ddC, zalcitabine; ddI, didanosine; DLV, delavirdine; DTG, dolutegravir; DRV, darunavir, EFV, efavirenz; ENF, enfuvirtide; ETR, etravirine; EVG, elvitegravir; FPV, fosamprenavir; FTC, emtricitabine; IDV, indinavir; LPV, loponavir; MVC, maraviroc; NFV, nelfinavir; RTV, ritonavir; RAL, raltegravir; RPV, rilpivirine; SQV, saquinavir; TDF, tenofovir; ZDV, zidovudine. Adapted from: Gallant, JE; Grant, P. Overview of Antiretroviral Agents. http://www.inpractice.com.

Over the last 15 years, ARV development has improved continuously (Figure 7). ARV drugs have become less toxic, more potent, and more convenient, increasing the feasibility of early and lifelong treatment. Some of the older regimens used in the past included up to 20 pills daily and today there are five regimens that involve one pill a day. With currently available ARV agents, 25 individual and 11 fixed-dose coformulations products (Table 1), is possible to design virologically suppressive treatment regimens for ARV-naive and most ARV-experienced patients. [27] In 2015, most HIV-1-infected persons initiating first-line ART are prescribed a once-daily, single-tablet regimen (STR) coformulations of ART, of which there are four options available. Currently approved coformulated ARV agents are shown on table 2.

Table 1. Antiretroviral agents approved by the FDA and in phase III clinical trials.

Approved Agents					
NRTIs	**PIs**	**NNRTIs**	**FI**	**EI**	**INSTI**
Abacavir	Atazanavir	Delavirdine*	Enfuvirtide*	Maraviroc	Elvitegravir
Didanosine*	Darunavir	Efavirenz			Dolutegravir
Emtricitabine	Fosamprenavir	Etravirine			Raltegravir
Lamivudine	Indinavir*	Nevirapine			
Stavudine*	Lopinavir/ritonavir	Rilpivirine			
TDF	Nelfinavir*				
Zidovudine*	Ritonavir				
	Saquinavir*				
	Tipranavir*				
Agents in Phase III Trials					
NRTIs	**PIs**	**NNRTIs**	**FI**	**EI**	**INSTI**
TAF					

*These agents are no longer in common usage in high-income countries. EI entry inhibitors, FI fusion inhibitors, INSTI integrase strand transfer inhibitors, NNRTI nonnucleoside reverse transcriptase inhibitors, NRTI nucleoside reverse transcriptase inhibitor, PI protease inhibitor, TDF tenofovir disoproxil fumarate, TAF tenofovir alafenamide fumarate.

Table 2. Currently approved coformulated antiretroviral agents.

Agent	**Dosing**
Abacavir/lamivudine/zidovudine**	1 in am; 1 in pm with/without food
Lamivudine/zidovudine**	1 in am; 1 in pm with/without food
Abacavir/lamivudine	1 daily with/without food
Emtricitabine/tenofovir DF	1 daily with/without food
Lopinavir/ritonavir	2 twice daily or 4 once daily with/without food
Atazanavir/cobicistat	1 daily with food
Darunavir/cobicistat	1 daily with food
Cobicistat/elvitegravir/emtricitabine/tenofovir DF*	1 daily with food (if creatinine clearance ≥ 70 mL/min)
Abacavir/dolutegravir/lamivudine *	1 daily with/without food
Efavirenz/emtricitabine/tenofovir DF*	1 daily at bedtime on empty stomach
Emtricitabine/rilpivirine/tenofovir DF*	1 daily with meal

*Single-tablet regimens.**These agents are no longer in common usage in high-income countries.

The choice of a regimen should consider individual needs and characteristics. Virologic efficacy, toxicity, tolerability, potential of drug-drug interaction, resistance testing results and cost issues influence the selection of an optimal regimen, as well as the presence of acute and chronic conditions. In the following sections we will focus on the four classes of ARV that are currently recommended for the majority of patients: NRTIs, NNRTIs, PIs, and INSTIs.

Nucleoside reverse transcriptase inhibitors

NRTIs appeared earlier and have been more widely used than other classes of ARVs, although older drugs within their classes were particularly toxic.[35] The NRTIs that are currently in common usage are abacavir (ABC), emtricitabine (FTC), lamivudine (3TC), and tenofovir (TDF). Tenofovir DF/emtricitabine (TDF/FTC) and abacavir/lamivudine (ABC/3TC) are available in fixed-dose coformulations and also as part of once-daily STR. Both combinations of NRTI plus a third agent are generally recommended by treatment guidelines in United States and Europe for initial therapy in ARV-naive patients. [18, 32, 33] They can effectively treat HIV-1 infection, but their toxicity profiles are different. ABC is associated with a hypersensitivity reaction,[36,37] which can be largely avoided with HLA-B*5701 screening. [37] An increased risk of myocardial infarction associated with ABC use has been reported.[38, 39] Cumulative use of tenofovir was independently associated with increased rates of chronic kidney disease, [40,41] loss of bone mineral density,[42] hypophosphatemic osteomalacia,[43] and increases in serum alkaline phosphatase levels.[44]

Because ABC/3TC and TDF/FTC may have a different impact on comorbidities, choosing between them could be helpful to customize the optimal therapy. Although ABC/3TC could be used like TDF/FTC in combination with the integrase inhibitor raltegravir (RAL) in virologically suppressed HIV-1-infected patients, there are no data comparing the two combinations of NRTIs in this setting.

Nonnucleoside reverse transcriptase inhibitors

NNRTI are common components of first-line HAART. There are four NNRTIs in common usage, nevirapine (NVP), efavirenz (EFV), rilpivirine (RPV) and etravirine (ETR). In general NNRTI have shown long-term efficacy and good long-term tolerability. [45, 46] One limitation to the use of first-generation NNRTIs NVP and EFV, is their low genetic barrier to the development of resistance and substantial cross-resistance. [47] Rash, ranging in severity from mild to life threatening, is a class adverse effect.

NVP was the first NNRTI introduced in clinical practice and is still widely used in resource-limited settings, where generic formulations are available. [26] NVP is associated with life-threatening hepatotoxicity that generally occurs during the first 18 weeks of therapy, as well as severe and potentially fatal skin reactions that may be part of a hypersensitivity reaction. In controlled trials, symptomatic hepatic events occurred in 4% of NVP recipients, and severe or life-threatening rash occurred in approximately 2% of patients. Although hepatotoxicity can occur in any patient, women and individuals with higher CD4+ cell counts are at greatest risk. [48]

EFV is one of the recommended regimens as initial therapy of HIV-1 infection for its long-term efficacy and safety data. Is available as a 1-pill once-daily regimen with TDF/FTC. Many patients develop central nervous system adverse effects such as drowsiness, insomnia, vivid dreams, and impaired concentration. These symptoms usually calm within 4 weeks, [49] although recent trials showed that the early central nervous system adverse effects of EFV may persist longer. [50, 51] Both NVP and EFV are metabolized via cytochrome P450 3A4 enzymes (CYP3A4) and subsequently have numerous important drug–drug interactions with other medications.

Second-generation NNRTI, ETR and RPV, were developed to improve the resistance profile and overcome the safety and toxicity limitations. [52, 53] The major advantage of ETR compared with the first-generation NNRTI agents is its activity against many NNRTI-resistant variants. In particular, the K103N mutation alone has not been shown to compromise the activity of ETR. For other NNRTI-associated mutations, a scoring system has been developed to predict response to ETR. [53] ETR is generally well tolerated with lower rates of rash in clinical trials when compared with other NNRTIs and lower rate of central nervous system adverse events when compared with EFV. [54]

RPV, is also available as a once-daily STR with TDF/FTC. In treatment-naive adults RPV demonstrated antiviral efficacy similar to that of EFV with regard to establishing virological suppression over 96 weeks of therapy in adults with baseline viral load (VL) ≤ 100000 copies/mL. RPV was generally well tolerated and appeared to have a more favourable tolerability profile than EFV. [55]

Protease inhibitors

PI/rs are indicated in combination with other ARV medications for both treatment-naive and treatment-experienced patients because of their proven virologic efficacy and high

barrier to resistance. [18, 33] In most cases, co-administration with either ritonavir (RTV) or cobicistat (COBI) is required to boost PI levels through inhibition of the CYP3A4, increasing the potential for drug-drug interactions. As a class, PIs are associated with gastrointestinal adverse effects, particularly nausea and diarrhoea and dyslipidaemia. Lipid changes consist in increases in fasting total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and very low-density lipoprotein cholesterol (VLDL-c) fractions and in triglycerides (TG), with minimal effect on high-density lipoprotein cholesterol (HDL-c) concentrations. [56, 57]

Early generation PI, particularly indinavir (IDV) and lopinavir/ritonavir (LPV/r) have been independently associated with a 12% to 16% increased relative risk of myocardial infarction (MI), per year of exposure. [58, 59] The two currently-recommended PI are atazanavir/ritonavir (ATV/r) and darunavir/ritonavir (DRV/r). [33] To date, ATV has not been associated with an increased incidence of cardiac or cerebrovascular events [60] while no similar analysis is available for DRV/r. Yet both of these PI produce elevations in total and LDL-c and TG in comparison with the integrase inhibitor RAL. [61]

Mechanisms other than lipids including chronic inflammation, [62, 63] endothelial dysfunction, [64, 65] insulin resistance, [66] and macrophage accumulation of cholesterol, [67, 68] have been suggested to contribute to the negative impact of PI/r on cardiovascular health. Increase in plasma lipids are usually associated with higher levels of inflammatory biomarkers in the general population, [69] therefore plasma biomarkers may help to assess the mechanisms involved in atherosclerosis pathogenesis. [70]

Integrase strand-transfer inhibitor - Raltegravir

RAL was the first INSTI, the most recent drug class, approved for use in HIV-1-infected patients. INSTI exhibit a novel mechanism of action against HIV-1 as they potently inhibit integrase enzyme, one of the three viral enzymes essential for HIV-1 replication. Raltegravir introduction revolutionized the management of multidrug-resistant viruses. [71] Currently, it has several potential applications. When used in combination with optimized background therapy allows treatment-experienced patients with multidrug-resistant virus and limited treatment options to achieve viral suppression. [72]

As a result of its efficacy, tolerability, and convenience, INSTIs are indicated in a variety of

clinical settings. It is appropriate for use in special populations given its favourable lipid profile, such as individuals with increased cardiovascular risks. It is also a good selection when drug interaction is an issue as for those on treatment for tuberculosis, chemotherapy, imunosupression or any treatment which impacts on cytochrome P450. Today is part of the preferred first-line regimens and is being studied as a significant part of drug class-sparing regimens. [18, 32, 33, 34]

INSTIs target the HIV-1 enzyme integrase, differently to proteases and polymerases, host cells have no integrase, thus RAL is not expected to have the same toxicity profile than other ARVs, although it may have its own particular adverse effects. [73] Indeed, studies have shown that RAL is effective and also well tolerated, has fewer neuropsychiatric, gastrointestinal and lipid-related effects compared to other commonly used agents, needs no food requirement and has hardly any drug interactions. [74, 75, 76] Most common related adverse effects are diarrhoea, nausea and headache. Drug discontinuation for adverse events is uncommon, as reported in studies of both naive and treatment-experiment patients. [71, 77, 78, 79]

Apart from being efficacious and have few adverse effects, RAL needs no food requirement and has no CYP3A4 interactions. From a convenience perspective, there could be disadvantages with RAL, as it is given twice daily. In this regard the results of ACTG 5257 turned that RAL regimen (despite being given twice daily) was either equivalent or superior to the PIs (DRV/r 800/100 mg once daily, or ATV/r 300/100 mg once daily) when considering both virologic success and tolerability. [80]

However, clinical trials and post-marketing surveillance in RAL-treated patients have reported laboratory abnormalities that could be an expression of skeletal muscle toxicity. In particular, transient elevations in serum creatine kinase (CK) have been described in association with RAL treatment, but they usually were self-limited and did not require treatment interruption or discontinuation. [71, 72, 79, 81]

Clinical myopathy, myositis and rhabdomyolysis appear to be very uncommon. Since its approval, in 2007, five isolated cases of myositis and rhabdomyolysis were associated with RAL.[82, 83, 84, 85, 86] Although a causal relationship with RAL has not been clearly established, the Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the manufacturer recommend using RAL with caution in individuals at increased risk of myopathy.[87] The incidence, clinical significance and risk factors are not well fully un-

derstood.

HIV-1 INFECTION, ANTIRETROVIRAL THERAPY, AND COMORBIDITIES

With the definitive success of ART in improving prognosis for persons living with HIV-1 infection, many people are aging with HIV. [88] Actually, thirteen per cent of the world adult population living with HIV-1 is aged 50 or older, [1] reaching more than 30 % of HIV-1 adult population in high-income countries. [4, 89] Consequently, age-associated comorbidities, such as hypertension, dyslipidaemia, diabetes, coronary artery disease, osteoporosis and malignancies, became increasingly important among HIV-1-infected people. In fact, more than half of HIV-1-infected patients aged ≥50 years have been reported to suffer from two or more concomitant noninfectious comorbidities (Figure 8).[8]

In this population, the presence of comorbidities may affects the tolerability and toxicity of ARV agentes. Treatment for these conditions often involves polypharmacy, which increases the risk of suboptimal adherence and the possibility of drug-drug interactions. Furthermore, some ARV agents may worsen comorbid conditions or increase the risk of

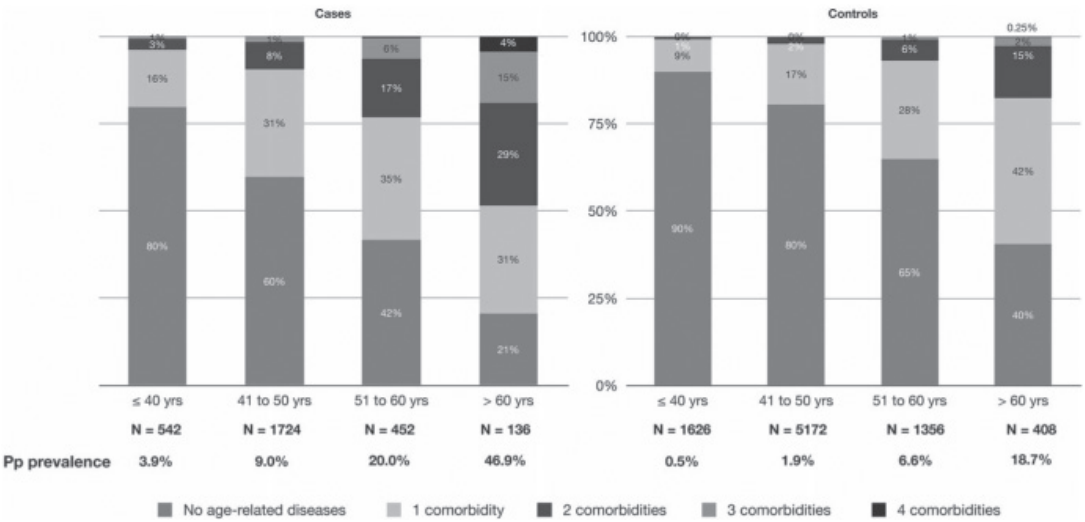

Figure 8. Prevalence of polypathology (Pp) defined as the simultaneous presence of ⩾2 noninfectious comorbidities among patients and control subjects, by age categories. The following comorbidities were included: hypertension, diabetes mellitus, hypothyroidism, cardiovascular disease, and bone fractures. Source: Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, Berti A, Rossi E, Roverato A, Palella F. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis. 2011 Dec;53(11):1120-6.

negative clinical outcomes. [18]

Cardiovascular disease in HIV-1-infected persons

Among the many noninfectious comorbidities, cardiovascular disease (CVD) have become of particular concern. For HIV-1-infected persons with access to effective combina-

tion ART, atherosclerotic cardiovascular disease is now a leading cause of morbidity and mortality. [90] ARV-induced metabolic changes, high prevalence of risk factors for CVD (e.g. smoking), and growing evidence on HIV-1-accelerated inflammatory processes are known to interact and promote atherosclerosis. [91] The majority of observational and retrospective data in treated and untreated patients support the proposition that HIV-1 infection is associated with an increase in accelerated atherosclerosis and CVD events. [8,91, 92, 93,94]

The relative contributions of HIV-1 and ART to CVD are subject of intense investigation. Untreated HIV-1 infection increases a number of factors that are known to be pro-atherogenic (Figure 9). HIV-1 persistence, permanent damage to mucosal lymphatic tissue with increased microbial translocation, and the presence of copathogens (e.g. cytomegalovirus) activate lymphocytes and monocytes and is associated with release of inflammatory cytokines and early vessel dysfunction. Subsequent coagulation and thrombotic activity, via cell damage and up-regulation of tissue factor pathways, platelet activation, or other mechanisms may contribute to premature atherosclerosis. Pro-atherogenic changes in lipids and lipoprotein metabolism are also consequences of both HIV-1 infection and

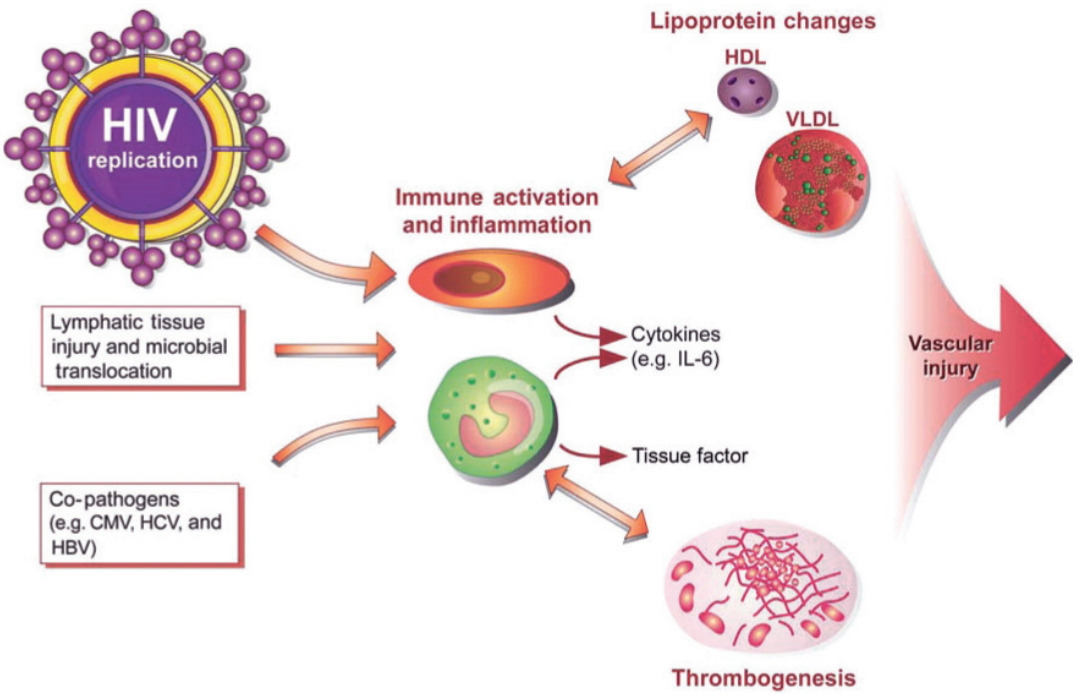

Figure 9. Pro-atherogenic factors related to untreated human immunodeficiency virus (HIV) infection. Adapted from: Baker JV, Lundgren JD. Cardiovascular implications from untreated human immunodeficiency virus infection. Eur Heart J. 2011 Apr;32(8):945-51.

chronic inflammation. [15]

The Strategic Management of AntiRetroviral Therapy (SMART) study, is a trial of intermit-

tent versus continuous use of ART as a strategy to reduce toxicities, including CVD risk.[96] In patients randomized to interrupt ART when their CD4+ cell count increased to > 250 cells/mm3 the relative risk for CVD events was 60% greater compared with patients who remained on continuous ART. Follow-up biomarker analyses demonstrated that D-dimer and interleukin-6 were associated with risk of death from all causes and individuals in the treatment interruption group experienced marked elevations in IL-6 and D-dimer levels. [11] Subsequently, increased concentrations of CRP, interleukin 6, and d-dimer were independently associated with CVD events in patients with HIV-1. [97]

ART has both positive and negative effects on cardiovascular risk. ART-related suppression of HIV-1 replication improves immune function and is associated with reductions in systemic inflammatory markers and risk for a CVD event, but is also associated with variable toxicity that may, itself, increase CVD risk. [98]

The D:A:D study, one of the largest observational trials on HIV and CVD with more than 30,000 patients in Europe, United States, and Australia, reported a 26% relative increase in the rate of MI per year of ARV exposure (95% CI: 1.12-1.41) during the first 4-6 years of treatment, after adjustment for demographic risk factors, including age (Figure 10). [99] A recent update from the D:A:D study has underlined the importance of traditional risk factors for CVD in HIV-1-infected patients. Across all the risk factors age contributed to the

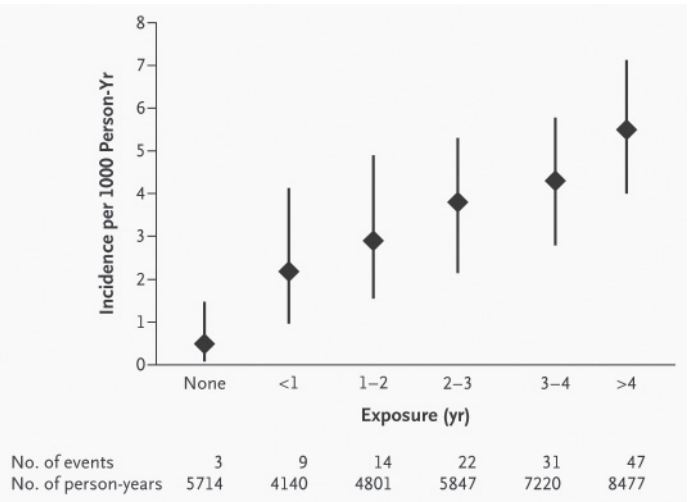

Figure 10. Incidence of myocardial infarction according to the duration of exposure to combination antiretroviral therapy. Source: Friis-Møller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med. 2003 Nov 20;349(21):1993-2003.

greatest increase in risk of CVD. [100]

Early reports of the D:A:D study identified an association between PI but not NNRTI use and CVD risk (relative risk per year: 1.16; 95% CI: 1.10-1.23). Risk was reduced, but remained significant, after adjustment for serum lipids, suggesting that the increased risk is not explained solely by drug effects on lipids (relative risk: 1.10; 95% CI: 1.04-1.18). [58] As already mentioned, further analysis of this cohort found that cumulative exposure to IDV and LPV/r, were associated with a significantly increased risk of MI. [59] No associations were found for nelfinavir, saquinavir with or without RTV, or for ATV. [60] Sufficient follow-up data have not been available to report on associations with darunavir.

Observational and retrospective cohorts have reported conflicting results for the association of ABC use with risk of MI. D:A:D reported 2-fold increased MI risk with ABC use (relative risk: 1.90, 95% CI: 1.47-2.45). [101] Other FDA and ACTG studies reported no increased risk for MI development among ABC recipients. [102,103] Additional information on ABC and MI risk has subsequently been reported, including studies that found no significant association between them, [104, 105, 106, 107, 108] as well as studies that support the observations in D:A:D. [109, 110, 111, 112, 113] Studies must be interpreted with caution because observational data are subject to bias and confounding factors, furthermore individuals initiating ABC are more likely to have many traditional MI risk factors vs. non-ABC users. [114]

The pathophysiology of coronary heart disease (CHD) in HIV-1-infected patients is very complex with a combination of conventional and emerging risk factors that are synergistic and interconnected. ART and HIV-1 itself could promote CHD through various pathophysiological pathways, together with environmental and genetic factors (Figure 11).

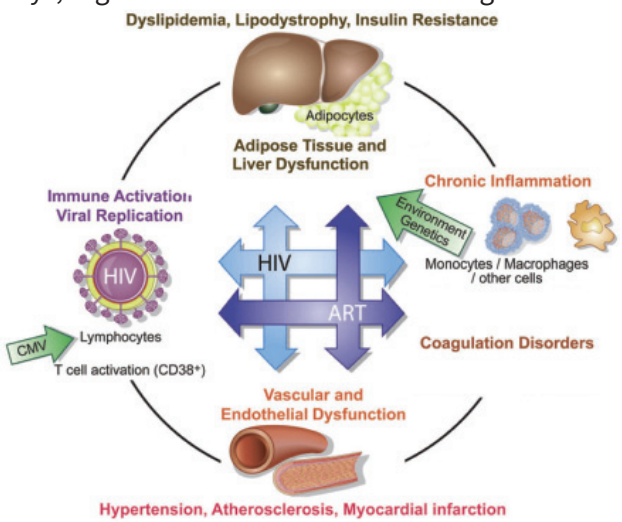

Figure 11. Hypothetical model for the pathogenesis of cardiovascular disease in HIV-infected persons. ART antiretroviral therapy; CMV cytomegalovirus. Adapted from: Hemkens LG, Heiner CB. HIV infection and cardiovascular disease. European Heart Journal (2014) 35, 1373–1381.

Both HIV-1 and ART have direct effects on adipose and liver function with subsequent dyslipidemia, lipodystrophy and insulin resistance. Persistent HIV-1 replication along with other viruses, e.g. cytomegalovirus leads to immune activation and chronic inflammation. Increased microbial translocation in the gut, is also associated with a chronic status of inflammation and coagulation disorders. Adipose tissue dysfunction, immune activation, and chronic inflammation have deleterious impact on endothelial cells and vascular smooth muscle cells leading to vascular and endothelial dysfunction with subsequent hypertension, atherosclerosis and myocardial infarction. [91]

Management of risk factors for cardiovascular disease

People living with HIV-1 are at increased risk of CVD [115] and therefore stratifying risk among this population and planning cardiovascular preventive strategies should be regularly done in all patients, especially in those receiving ART. Conventional cardiovascular risk equations do not take into account emerging cardiovascular risk factors such as inflammation, immune activation, coagulation disorders, kidney disease, HIV-1 itself, and ARV that have been associated with increased risk of MI or atherosclerosis, [91] which may underestimate risk in HIV-1-infected patients. [116] A cardiovascular risk calculator has been developed based on data from the D:A:D study that includes exposure to ARV with known increased risk of CVD. [100] Although the validation of this tool had some limitations [117] this instrument has been shown to predict the individual CVD risk marginally better than the established Framingham risk equation. [116]

The role for routine monitoring of surrogate markers of CVD in HIV-1 patients is not yet defined. Monitoring of inflammatory biomarkers and surrogate markers of CVD risk has been the subject of intense study, both to elucidate mechanisms associated with CVD and to identify the best markers of risk in HIV-1 patients. [118, 119] Impaired endothelium-dependent vasodilation is an indicator of atherosclerotic disease and can be assessed with a number of procedures, such as evaluation of carotid intima-media thickness, brachial artery flow-mediated dilation, and aortic pulse-wave velocity. Subclinical atherosclerosis has been reported in patients on ART, although traditional CVD risk factors remain the strongest predictors of risk compared to PI therapy and HIV-1 infection per se. [120, 121121] Data from cross-sectional studies on endothelial dysfunction suggest that validated surrogate markers may eventually serve to stratify and monitor high-risk patients. [122, 123, 124]

Given the high prevalence of traditional risk factors for CVD in HIV-1 individuals, man-

agement of dyslipidaemia, glucose abnormalities, hypertension and counselling for behaviour changes have become an important part of the overall care for patients living with HIV-1 infection. Management of such risk factors for CVD can, with few exceptions, be done according to the guidelines established for non-HIV infected individuals. [33, 125] A fasting lipid profile and screening for diabetes should be performed every 6-12 months in all patients, as well as before initiation of ART, and 1-3 months after ART initiation or switches. Frequent blood pressure monitoring is also advised. [91]

Rates of cigarette smoking among HIV-1-infected is 2 to 3 times higher compared to the general population. Prevalence of current smoking among HIV-1-infected varies from 40% to 70% across different studies. [126, 127, 128, 129] Accordingly, successful smoking cessation has been proved to reduce risk of CVD in HIV-1-infected persons. [130] Thus, smoking cessation efforts should be a priority in routine care of HIV-1-infected patients.

Increased lipid concentrations augment risk of CVD and therefore require concern, especially in patients with other associated factors. The patterns of dyslipidaemia change during the course of HIV-1 disease. Following HIV-1 infection, low levels of HDL-c and LDL-c predominate along with increase in TG levels. [131] Dyslipidemia that occurs during treatment for HIV-1 disease is characterized by increases in TC, LDL-c, and TG with HDL-c remaining low. The extent of lipid changes differs between ARV drugs and drug classes and the expected lipid disturbances is an important consideration when selecting a regimen.

PI-based therapy is generally associated with hypertriglyceridaemia and increases in LDL-c, [132] although lipid effects of different PIs may vary, especially regarding their effects on TG and HDL-c. [133, 134] Dyslipidaemia also has been associated with exposure to NRTIs, and lipid effects also vary across the NRTI class. TDF has less impact on lipid parameters than stavudine (d4T), zidovudine (ZDV) and also ABC. [42,135,] The favourable lipid influence of TDF in comparison with ABC was demonstrated in several studies. [136, 137, 138] Unfavourable lipid changes are also observed with agents from the NNRTI class. Increases in TC and TG are observed with use of EFV, particularly with longer duration of therapy. EFV was associated with greater lipid effects than NVP and ATV/r but with less hypertriglyceridemia than LPV/r [139, 137, 140]. Clinical trials investigating INSTI-based regimens have demonstrated that members of this class have little impact on lipid levels. [78, 50, 51, 141, 142]

Treatment of dyslipidemia in HIV-1-infected individuals receiving ART poses some particularities in relation to possible drug interactions with ARV drugs, since statins, PIs, and NNRTIs are all metabolized in the liver via CYP3A4 system. [143] Diet modifications, exercise,

maintaining normal body weight, reducing alcohol intake and stopping smoking are recommended as an initial step in management of dyslipidemia and CVD risk. In addition, guidelines for HIV-1 care that have addressed the management of dyslipidemia, recommend switching to a more lipid-friendly regimen, whenever feasible, and lipid-lowering therapy in second place. [33, 125] This strategy is best undertaken in patients in whom the lipid derangement is suspected to be the result of a specific ARV component.

For patients with elevated TC and LDL-c, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) are the preferred first-line therapy. HIV-1 guidelines recommend the use of statins that have fewer interactions with ART, such as pravastatin, but also atorvastatin and rosuvastatin. [144, 125] Choosing a drug is based on the presence of potential interactions and lipid lowering effective. Individual responses to statin therapy varied in

	ATV/r	DRV/r	LPV/r	EFV	ETR	NEV	RPV	MVC	DTG	EVG/c	RAL	ABC	TDF	FTC	3TC
Atorvastatin	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔
Fluvastatin	↔	↔	↔	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lovastatin	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔
Pravastatin	↔	↑	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Rosuvastatin	↑	↑	↑	↔	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔
Simvastatin	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔

Colour legend Pravastatin

No clinically significant interaction expected.
These drugs should not be coadministered.
Potential interaction which may require a dosage adjustment or close monitoring.
Potential interaction predicted to be of weak intensity. No dosage adjustment is recommended.

Text legend

↑ Potential increased exposure of the lipid-lowering drug.
↓ Potential decreased exposure of the lipid-lowering drug.
↔ No significant effect.

Figure 12. Drug interactions between lipid-lowering and antiretroviral drugs from the Liverpool HIV Pharmacology Group, University of Liverpool. Source: http://www.hiv-druginteractions.org/data/ExtraPrintableCharts/ExtraPrintableChartID8.pdf

the clinical trials and should be expected to vary in clinical practice (figure 12).

Lipid lowering effect is greater for rosuvastatin and atorvastatin and low to intermediate to pravastatin (Table 3). Simvastatin, and lovastatin, should not be administered with PIs due to potential for serious reactions and atorvastatin should be used with caution, increasing dose gradually to achieve the expected benefit . [145] Rosuvastatin undergoes minimal metabolism by CYP3A4 and has been shown to decrease LDL-c, reduce the atherogenic LDL phenotype, and reduce TG in HIV-1 patients. [146] In addition, switch strategies that employ ARVs with more favourable lipid profile are increasingly used as an intervention for ART-related dyslipidemia. [147, 148, 149] To our knowledge statins and PI/r switching

Table 3. High- moderate- and low-intensity statin therapy

High-Intensity Statin Therapy Daily dose lowers LDL–C by ≥50%	**Moderate-Intensity Therapy** Daily dose lowers LDL–C by 30% to <50%	**Low-Intensity Statin Therapy** Daily dose lowers LDL–C by <30%
Atorvastatin 40-80 mg Rosuvastatin 20 mg	Atorvastatin 10 -20 mg Rosuvastatin 5-10 mg Pravastatin 40-80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg	Pravastatin 10–20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

Adapted from: Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S1-45.

have not been compared using current generation statins and PIs.
Different strategies to minimize ARV-related effects on lipids and other intolerance or toxicity issues are discussed in the following section.

STRATEGIES TO LIMIT TOXICITY AND IMPROVE TOLERABILITY OF ART

New ARV are more effective, convenient, and better tolerated than past regimens increasing the feasibility of successful treatment even for patients with prior treatment failure and multidrug resistance. Once the goal of virological suppression has been accomplished, most patients will likely continue the same treatment without any need for change. However, for some, there are often important, nonvirologic reasons to modify their ARV regimen. [150]

The advances in HIV-1 treatment and the understanding about drug resistance enabled to consider different strategies to minimize toxicity and maximize adherence. Multiple therapeutic switch options are now available for patients on suppressive ART with varying efficacies and effects on treatment-associated adverse events (Table 4). When modification is necessary, the first goal of the new regimen should always be to maintain viral suppression. Yet, must be managed with caution and should only be done when potential benefits outweigh the potential risks. Critical factors to consider in the selection of a new regimen include consideration of the history of previous ARV drug exposure, current drug resistance patterns, other drugs with the potential for drug interactions, and individual comorbid conditions. [18, 32]

Modifying PI/r regimens in virologically suppressed patients

Most common nonvirologic reasons to modify a PI/r–containing regimen are gastrointestinal adverse effects, dyslipidemia, risk of drug interactions with RTV, and need for regimen simplification.

Switch from a higher to a lower dose of ritonavir

When an HIV-1-infected patient is experiencing adverse events associated with the use of RTV, one strategy is to switch to a regimen with lower dose of RTV. In the ATAZIP study switching to ATV/r was noninferior in maintaining virologic suppression with significant decreases in TG, TC level, and TC:HDL ratio compared with continuing the LPV/r regimen. More patients in ATV/r arm experienced hyperbilirubinemia compared with those in the LPV/r arm (17% and 2%, respectively). However, adverse events resulting in treatment discontinuation were similar in each arm (5%). [151]

Switch from a PI/r to unboosted ATV

Even low doses of RTV can be a source of adverse events, therefore switching patients with virologic suppression on a PI/r–based regimen to unboosted ATV might be of interest. In the ARIES trial, 515 treatment-naive patients with HIV-1 RNA < 50 copies/mL and no evidence of virologic failure during a 36-week induction phase of ATV/r plus ABC/3TC were randomized to switch to unboosted ATV or to continue the induction regimen. After 48 weeks, changes in median lipid levels from randomization were more favourable with ATV vs. ATV/r, as was the incidence of hyperbilirubinemia (4% vs. 10%). [152] Virologic suppression rates were similar between groups, even at 144 weeks, 77% of patients who switched to unboosted ATV vs. 73% of patients who continued the induction regimen. [153] Other studies have reported similar benefits of switching to unboosted ATV. [154, 155, 156] However, it should be noted that unboosted ATV cannot be combined with tenofovir. The ASSURE trial evaluated regimen simplification in 296 HIV-1-infected patients with TDF/FTC plus ATV/r to a regimen of ABC/3TC plus unboosted ATV. There were significant reductions in bone and renal biomarkers with maintained virologic suppression. [157]

Switch from a PI/r to NRTI or NNRTI

Switching from a PI/r to NNRTI in patients receiving a virologically suppressive regimen is a valuable option for prevention or improvement of metabolic and gastrointestinal toxicity and regimen simplification. NVP and RPV have the advantage of their metabolic profile. A meta-analysis of clinical trials evaluating the switch from suppressive PI-based

regimens to NVP-based regimens concluded that switching to NVP is virologically and immunologically safe. [158] Although not found in all studies, one advantage of switching from a PI to NVP is an improved lipid profile. [159]

EFV and RPV have the advantage of being available as once-daily STR. In a study with 300 patients on stable ART (NNRTI or PI based) without previous virologic failure patients were randomized to switch to coformulated TDF/FTC/EFV or to continue their current regimen. [160] The results demonstrated noninferiority of TDF/FTC/EFV through 48 weeks compared with baseline ARV regimen (88% vs 89%, respectively). Added benefits of the switch to the single pill combination included improvements in triglycerides levels and quality-of-life measurements. In the SPIRIT trial, a randomized, 48-week switch study, 476 virologically suppressed patients switching to the single pill TDF/FTC/RPV from PI/r regimen maintained virologic suppression with a low risk of virologic failure, while improving TC, LDL-c, and TG. [161]

NNRTIs have a low genetic barrier to resistance and must be supported by an active background regimen. Switching from a PI/r to an NNRTI must follow strict selection criteria to ensure that patients do not harbour NRTI resistance mutations which increases risk of virologic failure. [147] Use of triple NRTIs is no longer recommended in any clinical situation, including switch scenarios, according to current guidelines, for its reduced efficacy. [18, 33]

Switch from PI/r to an INSTI

Studies evaluating switch on virologically suppressed patients receiving stable PI/r-based ART to an INSTI found improvements in serum lipids. The SPIRAL study, explored the strategy of switching from a PI/r to RAL or to continue on PI/r-based therapy. Switching to RAL resulted in a better lipid profile than continuing PI/r while sustaining noninferior efficacy at week 48, even in patients who had experienced previous virologic failure (Figure 13). [148] SWITCHMRK 1 and 2 studies which randomized patients suppressed on stable on LPV/r-based ART with ≥ 2 NRTIs to switch to RAL or continue their original regimen, showed greater percentage changes in lipid concentrations from baseline in the switch arm. The study had to be early stopped at week 24, since RAL failed to meet the protocol-defined criteria for noninferiority. [149]

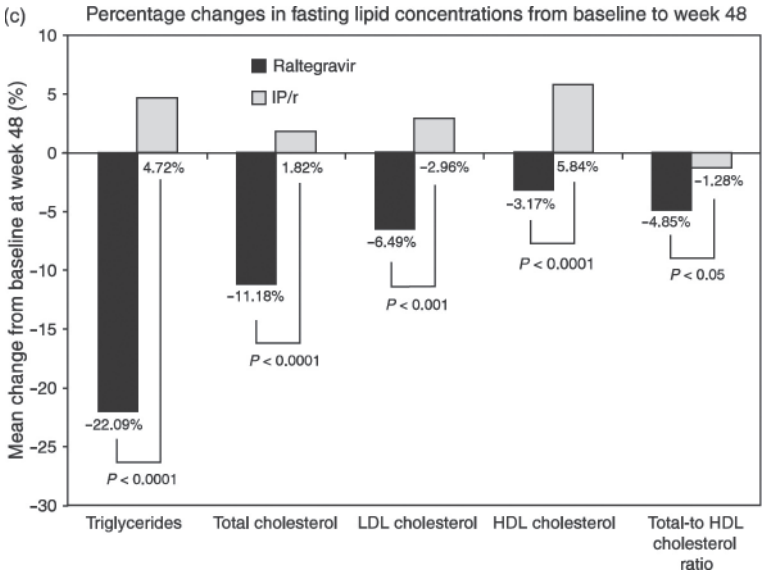

Figure 13. Percentage changes in fasting lipid concentrations from baseline to week 48. LDL low-density lipoprotein cholesterol, HDL high-density lipoprotein cholesterol, lP/r ritonavir-boosted protease inhibitor.

Although it is not clear why the result of these studies differed, one possible explanation is the longer duration of virologic suppression required as an inclusion criteria in SPIRAL. Some of these patients may have had underlying NRTI resistance and, therefore, awareness of treatment history and resistance profile is crucial to evaluate the activity of the background regimen to support RAL. [18, 33]

The STR of elvitegravir/COBI/TDF/FTC (EVG/COBI/TDF/FTC) is currently included as a recommended first-line regimen for treatment-naive patients with estimated creatinine clearance ≥ 70 mL/min. [18, 33] Recently, a multicenter, prospective, randomized, open-label phase III trial, the STRATEGY-PI study, evaluated efficacy and safety of switching to single-tablet, once-daily EVG/COBI/TDF/FTC from PI/r plus FTC/TDF regimens. Switching from LPV/r resulted in decreases in TC, TG, and HDL-c with 94% of patients who switched maintaining HIV-1 RNA < 50 copies/mL vs. 87% of patients in the control arm. This approach appeared to be well tolerated with no cases of renal tubulopathy and no treatment-emergent resistance. In addition, switching to the STR was associated with a decrease in diarrhoea and bloating from baseline to week 48. [162]

It is well known that integrase inhibitors, particularly RAL, have been associated with greater reduction in lipids following replacement from a PI/r while sustaining virological suppression in plasma. Whether this approach has an impact on other mechanisms involved in the pathogenesis of atherosclerosis, such as inflammatory and coagulation biomarkers, require further study.

Switch to a ritonavir-sparing and NRTI-sparing regimen

Although it is desirable to use always the most potent available ART regimen for treatment of HIV-1 infection, in clinical practice ARV choices including NRTIs or PIs may be challenging for some patients. In select circumstances a clinician may decide to switch a patient who has achieved virologic suppression to a less potent agent or regimen or with a lower genetic barrier to resistance. Furthermore, nowadays efficacy is less of a problem compared with previous times. Indeed, a large proportion of ARV-naive patients achieve undetectable HIV-1 RNA in plasma (less than 50 copies/mL) after starting ART. [27]

In contrast, the contributions of ART to the development and progression of comorbidities have gained increasing importance as HIV-1-infected patients are getting older. In a context of a patient with high risk of CVD or a positive HLA-B*5701 assay, who also has osteoporosis or chronic kidney disease, an alternative regimen avoiding NRTI, may be the optimal regimen. Secondly, regimens that include PI/r have a greater pill burden, and are associated with mild to moderate nausea, diarrhoea, and dyslipidaemia, even though these adverse effects occur less frequently with newer PIs. In those circumstances, a new regimen that excludes both PI/r and NRTIs might be considered. In these situations, it is important to consider the possibility of archived HIV-1 resistance mutations and the requirement for a high level of adherence to the new regimen.

New ARVs, such as the integrase inhibitor, RAL, and the NNRTI, ETR, have not shown major limiting toxicities, are effective in patients with prior resistance to NRTIs and PIs and pose a low risk of clinically significant drug interactions. [71, 163] The results of a small retrospective study evaluating the switch from different ART regimens to RAL plus ETR in 18 patients with virologic suppression have demonstrated promising early findings. [164]

Another study evaluated RAL in combination with ATV in 25 HIV-1-infected adults. After week 48, all were found to have maintained undetectable HIV-1 RNA, no serious adverse events were identified, and no patient discontinued therapy due to adverse events. [165] It is worth noting that the SPARTAN study, although not a switch study, demonstrated an increased incidence of grade 3/4 hyperbilirubinemia and an unacceptably high incidence of integrase resistance at virologic failure in the experimental arm with unboosted ATV 300 mg plus twice-daily RAL 400 mg. [166]

Recent data from the LATTE study that evaluated a treatment simplification strategy based on GSK1265744, an investigational INSTI and dolutegravir analogue may provide useful information on future PI/r- and NRTI-sparing switch strategies. In treatment-naive patients an induction regimen consisting of GSK1265744 plus 2 NRTIs, followed by maintenance GSK1265744 plus RPV, resulted in similar virologic suppression rate as EFV plus 2 NRTIs over 48 weeks. In addition, GSK1265744 was well tolerated and associated with fewer discontinuations due to adverse events than EFV. [167] Based upon these considerations, for carefully selected patients a dual therapy based on ETR plus RAL is worthy to be investigated.

Treatment simplification strategies

As already mentioned, PI have been substantially involved in the toxicity and tolerability issues. However, agents form this class have a very high genetic barrier to resistance and multiple viral mutations are required to reduce their activity, suggesting they can maintain virologic suppression without the need for 2 other drugs. Maintenance of virologic suppression with PI/r monotherapy (PIMT) is an investigational therapeutic strategy that takes advantage of this high genetic barrier to resistance, it allows to prevent toxicity associated with NRTIs, simplifies some regimens, lowers costs and preserves newer drugs for future use in case of resistance related to drug failure.

PIMT has been tested in different settings and the data on simplification strategies to PI/r alone after virologic suppression have been diverse. In combination, some studies have demonstrated maintenance of virologic suppression with PIMT after suppression with a standard regimen, while other studies suggest more low-level viremia, virologic failure, and detectable virus in the cerebrospinal fluid than standard 3-drug therapy. [168, 169, 170, 171] Although, the overwhelming majority of failing patients regained virological suppression following reintensification with 2 NRTI (165). [172, 173, 174]

Focusing on switch studies, data on DRV/r [172, 173] and LPV/r [175, 176], showed efficacy as a maintenance strategy in patients with prior suppression, while studies on ATV/r do not recommend its use as monotherapy due to higher rates of viremia compared with triple therapy. [177, 178] On the other hand, it has not shown sufficient efficacy in patients with detectable VL, either in naive patients or as second-line therapy. [154, 179, 180]

In aggregate, all studies have similar limitations: the number of included patients is relatively small and the results may not be generalized as they have different inclusion criteria. Selection criteria for PIMT applied to a clinic population in Spain identified 17% of patients suitable for this approach. [181] At present, PIMT is accepted as an alternative regimen in some HIV-1 treatment guidelines, especially in patients showing NRTI-related toxicity, although only in patients without history of failure on prior PI based therapy, with undetectable VL for at least 6 months and excellent adherence. [18, 33]

Modifying NRTIs in virologically suppressed patients

ZDV and d4T are no longer recommended for use in current ART regimens, but there are patients who still receiving a thymidine analogue since many years. [18] The strategy for these patients, in general is to switch to TDF or ABC. There is evidence demonstrating the benefits of switching from thymidine analogues to TDF or ABC in virologically suppressed patients. [113, 182, 183] Regarding second generation NRTI, studies have demonstrated improvements in lipids when switching from ABC/3TC to TDF/FTC. [138, 184]

Modifying NNRTIs in virologically suppressed patients

A few studies have examined the efficacy of switching NNRTIs in virologically suppressed patients because of toxicity and dosing complexity. The largest study is the STRATEGY-NNRTI in which virologically suppressed patients were switch from an NNRTI plus TDF/FTC to EVG/COBI/TDF/FTC. Among 439 patients, 290 were randomized to switch regimens. At the Week 48 the single-tablet integrase inhibitor regimen was noninferior to continuing the NNRTI-containing regimen. In addition switching from an EFV-based regimen to the STR was associated with decreased rates of neuropsychiatric symptoms. Virologic failure rates were 1% in both arms, and there was no treatment-emergent resistance. [186]

The results of an open-label trial indicate that switching from EFV to RPV may be a safe option for patients who cannot tolerate EFV. [187] In an ACTG study, switching from EFV to NVP for toxicity was generally safe. [188] In another study, patients who switched to NVP experienced significant decreases in their low-density lipoprotein cholesterol after 1 year, compared to patients who maintained EFV. [189] Switching from EFV to ETR in virologically suppressed patients due to toxicity has also been studied. ETR maintained virologic suppression and patients randomized to the ETR arm experienced significant reductions in grade 2-4 central nervous system adverse events vs patients who continued EFV. [190]

Switch from enfuvirtide to RAL

ENF is a potent agent in patients with multidrug-resistant HIV-1, availability of more convenient and better-tolerated alternatives has limited its use. In virologically suppressed patients, ENF can be safely switched to RAL. [191]

Switch versus treatment for dyslipidemia

Replacing an implicated drug by another that is better indicated and exhibits similar potency is a strategy applied to handle complications such as an adverse event or drug interaction or to maximize the potential for optimal adherence. Nevertheless, for treatment-experienced patients with underlying resistance mutations this approach may not be feasible. In these situations, it may be appropriate to treat the adverse effect and maintain the ARV regimen.

Hypercholesterolaemia associated with PI/r may be managed by lipid lowering therapy, such as statins, or by replacing the PI/r with an alternative ARV with fewer lipids effects. Switching from a PI/r for hyperlipidaemia is generally safe and effective in virologically suppressed patients. Studies using a switch strategy from a PI/r to RAL have shown substantial improvement in lipids. [148, 149] However, not all switches are completely successful. Switching potentially removes the underlying cause of dyslipidaemia, but also carries the possibility of losing virological control, as demonstrated in switch studies from a PI/r to RAL, in which a compromised NRTI back bone increased the risk of treatment failure. [149] In this situation the activity of the accompanying drugs is a key determinant of outcome.

The efficacy of statins in reducing serum lipids and in preventing cardiovascular events amongst the general population has been established in multiple trials.[192, 193] Adding a statin may, however, introduce new adverse events (e.g. myopathy) and increase pill burden, cost, and risk of drug interactions. Ultimately, intervening for hypercholesterolaemia will only be of clinical relevance if those treated have elevated cardiovascular risk.[194]

Although both statin therapy and PI/r switching lower total and non-HDL cholesterol and triglyceride levels [148, 149, 195, 196] only one randomized study has compared these two approaches [197]. The interventions employed in this study, pravastatin or bezafibrate, were each more effective than PI/r switching for reducing lipid levels over a 12-month period. The PIs included are no longer recommended, also the options for ARV switch were limited at that time, statins used were less potent and cardiovascular risk reduction was not evaluated.

BRIEF OUTLINE OF THE THESIS

In summary, modifying regimens in the setting of viral suppression is an approach that can be contemplated to simplify treatment and improve adherence by reducing pill burden and dosing frequency, to prevent short or long-term toxicity and enhance tolerability, to minimize or address drug interaction, but also to preserve future treatment options and even to reduce costs in particular settings.

PI/r have a very high genetic barrier to resistance and multiple viral mutations are required to reduce their activity, suggesting they can maintain virologic suppression without the need for 2 other drugs. PIMT has been tested in different clinical trials, but not in clinical

practice, and data reported have been diverse. However, agents form this class have been substantially involved in tolerability and toxicity issues, especially lipid toxicity.

RAL, have been associated with greater reduction in lipids following replacement from a PI/r while sustaining virological suppression in plasma. Whether this approach has an impact on other mechanisms involved in the pathogenesis of atherosclerosis, such as inflammatory and coagulation biomarkers, requires further study. Although ABC/3TC and TDF/FTC could be equally used in combination with RAL, there are no data comparing the two combinations of NRTIs in virologically suppressed HIV-1-infected patients switching from PI/r to RAL.

Replacing a PI/r for dyslipidaemia potentially removes the underlying cause, but also carries the possibility of losing virological control. In this situation, it may be appropriate to manage hypercholesterolaemia associated with PI/r with lipid lowering therapy, such as statins. Another strategy to avoid adverse effects associated with PI/r and NRTI is a ritonavir-sparing and NRTI-sparing regimen, such as dual therapy with ETR/RAL.

Finally, RAL is known to be effective and well tolerated and currently has several applications for treatment of HIV-1 infection. However, post-marketing surveillance have reported laboratory abnormalities that could be an expression of skeletal muscle toxicity. The potential causal relationship of RAL with muscle toxicity in clinical practice deserves additional investigation.

This thesis is presented as a compendium of articles according to the regulation adopted by the Commission of the Doctoral Program “Medicine” at the University of Barcelona. Six strategies to optimize treatment for HIV-1 infection in adults with sustained virological suppression are evaluated, in the following articles:

1. Effectiveness and tolerability of PIMT in the clinical practice.
2. Changes in cardiovascular biomarkers in ART-experienced patients switching from PI/r to RAL.
3. Efficacy and safety of ABC/3TC vs. TDF/FTC in ART-experienced patients switching from PI/r to RAL.
4. Efficacy and safety of rosuvastatin vs. PI/r switching for treatment of hypercholesterolaemia in adults with increased cardiovascular risk.
5. Efficacy and safety results of a pilot study with ETR plus RAL in ARV-experienced patients .
6. Incidence and risk factors for RAL associated CK elevation in clinical practice.

HYPOTHESIS

HIV treatment can be simplified in antiretroviral-experienced patients by improving the tolerability and reducing toxicity with new drugs and new strategies without compromising virological efficacy.

OBJECTIVES

The main objective of this thesis is to evaluate new strategies to limit treatment complications and to assess safety considerations aiming to improve antiretroviral tolerability in HIV-1-infected adults with sustained virological suppression. Secondary objectives are:

1: To evaluate the effectiveness and tolerability of ritonavir-boosted protease inhibitor monotherapy and predictors of virological failure in clinical practice.
2: To assess changes in cardiovascular biomarkers in virologically suppressed patients switching from ritonavir-boosted protease inhibitor to raltegravir.
3: To compare the efficacy and tolerability of abacavir/lamivudine and tenofovir/emtricitabine, in virologically suppressed patients switching from ritonavir-boosted protease inhibitor to raltegravir.
4: To compare the hypolipidemic efficacy of ritonavir-boosted protease inhibitor switch vs. statin therapy for hypercholesterolaemia in HIV-infected patients with increased cardiovascular risk.
5: To investigate the efficacy and safety of a new dual therapy with etravirine plus raltegravir in antiretroviral-experienced HIV-1-infected patients.
6: To determine the incidence and risk factors for creatinine kinase elevation in HIV-1-infected patients receiving raltegravir-containing regimen.

ARTICLE 1

Effectiveness of ritonavir-boosted protease inhibitor monotherapy in the clinical setting: same results as in clinical trials? The PIMOCS Study Group.

Adrian Curran[1], Polyana Monteiro[2], Pere Domingo[3], Judit Villar[4], Arkaitz Imaz[5], Esteban Martínez[2], Irene Fernández[3], Hernando Knobel[4], Daniel Podzamczer[5], Jose Antonio Iribarren[6], María Peñaranda[7] and Manuel Crespo[1] on behalf of the PIMOCS Study Group.

[1]Infectious Diseases Department, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona; [2]Infectious Diseases Department, Hospital Clinic i Provincial, Barcelona; [3]Infectious Diseases Department, Hospital Universitari Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona; [4]Infectious Diseases Department, Hospital del Mar, Barcelona; [5]HIV Unit, Infectious Diseases Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat; [6]Infectious Diseases Unit, Hospital de Donosti, San Sebastian; [7]Infectious Diseases Unit, Hospital Universitari Son Espases, Palma de Mallorca.

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Effectiveness of ritonavir-boosted protease inhibitor monotherapy in the clinical setting: same results as in clinical trials? The PIMOCS Study Group

Adrian Curran[1]*, Polyana Monteiro[2], Pere Domingo[3], Judit Villar[4], Arkaitz Imaz[5], Esteban Martínez[2], Irene Fernández[3], Hernando Knobel[4], Daniel Podzamczer[5], Jose Antonio Iribarren[6], María Peñaranda[7] and Manuel Crespo[1] on behalf of the PIMOCS Study Group†

[1]Infectious Diseases Department, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain; [2]Infectious Diseases Department, Hospital Clínic i Provincial, Barcelona, Spain; [3]Infectious Diseases Department, Hospital Universitari Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain; [4]Infectious Diseases Department, Hospital del Mar, Barcelona, Spain; [5]HIV Unit, Infectious Diseases Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Llobregat, Spain; [6]Infectious Diseases Unit, Hospital de Donosti, San Sebastian, Spain; [7]Infectious Diseases Unit, Hospital Universitari Son Espases, Palma de Mallorca, Spain

*Corresponding author. Tel: +34-932746090; Fax: +34-934894091; E-mail: acurran@vhebron.net
†Members of the PIMOCS Study Group are listed in the Acknowledgements section.

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Objectives: Ritonavir-boosted protease inhibitor monotherapy (PIMT) is a maintenance strategy that prevents nucleoside reverse transcriptase inhibitor toxicity and reduces costs. Some trials compare PIMT with combined antiretroviral therapy, but restricted selection criteria and low sample size hamper data extrapolation to routine practice. Here, we analyse the effectiveness and safety of PIMT in clinical practice.

Methods: This was a retrospective, observational, multicentre study. Adult HIV-1 patients receiving PIMT with darunavir or lopinavir were included. A Cox regression model identified independent predictors for virological failure (VF).

Results: A total of 664 patients (435 on darunavir/ritonavir and 229 on lopinavir/ritonavir) [74% male, median age of 54 years, one-third with previous protease inhibitor VF, CD4 nadir 189 cells/mm^3 and 42% coinfected with hepatitis C virus (HCV)] were analysed. After a median follow-up of 16 months, 78% of patients (95% CI 74%–81%) remained free from therapeutic failure (TF) (change between ritonavir-boosted PIs not considered failure). At 12 months, by intention-to-treat analysis (change between ritonavir-boosted PIs equals failure), 83% of patients were free from TF (87% darunavir/ritonavir versus 77% lopinavir/ritonavir, $P=0.001$). Regarding VF, 88% of patients maintained viral suppression at 12 months (93% darunavir/ritonavir versus 88% lopinavir/ritonavir, $P=$ not significant). CD4 nadir <200 cells/mm^3 [hazard ratio (HR) 1.58, 95% CI 1.01–2.49] and undetectable viral load prior to PIMT <24 months (HR 1.86, 95% CI 1.20–2.91) were independent predictors for VF. Prior protease inhibitor failure, HCV coinfection and the protease inhibitor/ritonavir used were not associated with PIMT outcome. A total of 158 patients stopped PIMT, 6% due to adverse events. Two patients developed encephalitis.

Conclusions: PIMT effectiveness was consistent with data from clinical trials. Viral suppression duration prior to PIMT and CD4 cell count nadir were independent predictors for PIMT outcome.

Keywords: HIV, monotherapy, protease inhibitors, darunavir, lopinavir

Introduction

With the widespread use of combined antiretroviral therapy (cART), HIV morbidity and mortality have significantly decreased in the last decade. However, adverse events associated with some antiretroviral drugs, such as mitochondrial toxicity with thymidine analogues[1] or kidney and bone concerns with tenofovir,[2,3] have limited their use. At the same time, newer drugs with higher potency and better tolerability have become available. This has entailed the investigation of new strategies in treating HIV infection.

One of these strategies is ritonavir-boosted protease inhibitor monotherapy (PIMT), supported by the high potency and genetic barrier of this family. In addition to preventing the toxicity

associated with the use of nucleoside reverse transcriptase inhibitors (NRTIs), PIMT simplifies some antiretroviral regimens, lowers costs and preserves newer drugs for future use.

PIMT has been tested in different settings. It has shown non-inferior efficacy as a switch strategy in some studies and is accepted as an alternative regimen in some HIV treatment guidelines, especially in patients showing NRTI-related toxicity, although only in patients without history of failure on prior protease inhibitor-based therapy, undetectable viral load for ≥6 months and excellent adherence.[4,5] On the other hand, it has not shown sufficient efficacy in patients with detectable viral load (either in naive patients[6,7] or as salvage therapy[8]) or as an induction–maintenance strategy.[9]

Focusing on switch studies, there are data mainly with ritonavir-boosted darunavir[10,11] and lopinavir[12,13] having shown their efficacy in this setting. There are also data with atazanavir,[14,15] but the results do not recommend its use as PIMT. We have scarce data with other protease inhibitors that are seldom used nowadays.[16–18] However, all PIMT studies have similar limitations: the number of included patients is relatively small and the results are not generalizable as they have different inclusion criteria.

The aims of this study are to describe the characteristics of patients receiving PIMT in the clinical setting, to analyse the effectiveness and tolerability of these regimens in patients who might differ from those included in clinical trials and to analyse if there are any parameters that can help to predict virological failure (VF) with PIMT in daily practice.

Methods

This was a retrospective, observational, multicentre study carried out in seven Spanish university hospitals.

Adult patients (≥18 years old) with HIV-1 infection, currently receiving or having received at any time PIMT with lopinavir/ritonavir or darunavir/ritonavir, were selected from each centre's HIV-infected patients database and evaluated for study inclusion. Their clinical charts and electronic medical records were reviewed to obtain relevant data. The database was closed for analyses on 31 December 2012. Participation in clinical trials was not an exclusion criterion. Patients with detectable HIV viral load at PIMT initiation or with no available viral load measurements while on PIMT were excluded from the study analysis.

Demographic data (age, sex and race), HIV-related data (transmission risk factor, years of infection, previous antiretroviral regimens and reasons for discontinuation and prior resistance testing) and hepatitis C virus (HCV) coinfection status were recorded for each patient. All previous resistance tests were taken into account to determine the potential susceptibility to antiretrovirals. Drug resistance-associated mutations (RAMs) were considered as defined by the International AIDS Society—USA guidelines.[19] Frequency of follow-up visits was decided by the physician in charge of the patient. Information regarding CD4, HIV RNA, adverse events or reasons for discontinuing PIMT was recorded. If PIMT was stopped, the results of resistance testing when performed, the subsequent prescribed therapy and the outcomes with the new treatment were analysed.

VF was defined as two consecutive viral loads >50 copies/mL or a single determination >50 copies/mL if the treatment was changed or the patient was lost to follow-up (defined as not attending appointments and not collecting the antiretroviral treatment at the hospital pharmacy). Therapeutic failure (TF) included VF, antiretroviral therapy change due to adverse events or any other reason, death or loss to follow-up.

The primary objective of the study was to analyse the effectiveness of PIMT in the clinical setting, defined as the percentage of patients with no TF during the study period.

Secondary objectives were to describe the characteristics of patients receiving PIMT outside clinical trials, analyse the effectiveness of PIMT regarding VF, describe the evolution of HIV-related laboratory parameters (CD4 cell counts and HIV RNA blips), describe the safety of and reasons for stopping PIMT, investigate predictors for VF with PIMT and describe the outcome in case of TF. We also wanted to compare treatment outcomes between darunavir/ritonavir and lopinavir/ritonavir, the two ritonavir-boosted PI combinations currently accepted as PIMT in some guidelines.[4,5]

The study protocol was approved by the institutional review boards of the participating centres and written informed consent was obtained from all patients.

Statistical analyses

For quantitative variables, medians and IQRs were used as measures of central tendency and dispersion. Numbers of patients and percentages were given for qualitative variables.

The changes from baseline (period of time between starting and stopping PIMT for any reason or closing of the database, whichever occurred first) were compared using the paired Student's *t*-test for quantitative variables. Comparisons between quantitative non-paired variables were performed with Student's *t*-test and the χ^2 test was used for qualitative variables.

For the primary PIMT effectiveness endpoint, we performed a modified intention-to-treat analysis (mITT: stopping or changing PIMT due to any reason equals failure, except for changes from one PIMT to another PIMT, censoring data at treatment change). For other effectiveness endpoints, an ITT analysis was used (VF, stop or change for any reason equals failure).

An on-treatment analysis of effectiveness (censoring any cause of TF apart from VF) was also performed.

Kaplan–Meier curves were used to estimate the time to TF and VF (censoring data at 24 months of follow-up as very few patients receiving darunavir/ritonavir were treated for longer than this timepoint). The log-rank test was used to compare ritonavir-boosted PIs.

Cox proportional hazards regression was used to identify predictive factors for VF. Variables associated with VF in univariate analysis ($P<0.2$) and clinically relevant variables were considered for inclusion in the multivariate models.

All statistical tests were two-tailed and were performed at a level of statistical significance of 0.05. SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

Initially, 725 patients who started PIMT between January 2004 and July 2012 were evaluated. Of them, 664 patients fulfilled the inclusion criteria and were analysed (Figure 1). The baseline characteristics and prior antiretroviral treatments of the patients included in the analysis are shown in Table 1. The median (IQR) CD4 nadir was 189 (76–297) cells/mm^3 and 199 (30%) and 110 (17%) patients had CD4 nadirs <100 and <50 cells/mm^3, respectively. The median time with undetectable viral load prior to PIMT initiation was 49 (24–83) months and the percentage of patients with <6, <12 and <24 months of undetectable viral load was 7%, 14% and 26%, respectively. Most patients (90%) had been previously exposed to a protease inhibitor and one-third of them had experienced VF on a protease inhibitor-containing regimen. The protease inhibitors on which patients had previously failed included both old non-ritonavir-boosted protease inhibitors (indinavir and nelfinavir) and newer ritonavir-boosted protease

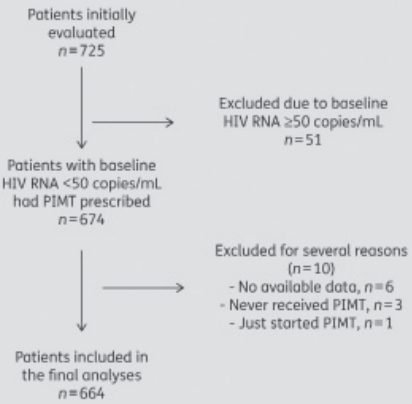

Figure 1. Patient flow chart.

inhibitors (atazanavir, fosamprenavir, lopinavir and saquinavir) in the same proportion (17% in each category).

Effectiveness

Patients were followed for a median of 16 (11–24) months on PIMT. Patients receiving lopinavir/ritonavir had a significantly longer follow-up compared with those receiving darunavir/ritonavir [21 (10–40) versus 15 (11–20) months, $P<0.001$].

Overall, by mITT analysis, 78% of patients (516/664, 95% CI 74%–81%) remained free from TF at the end of follow-up. By ITT analysis, cumulative survival at 12 months was 83.1% (453/545, 95% CI 80%–86%); 87.2% (293/336, 95% CI 83%–91%) for darunavir/ritonavir and 76.6% (160/209, 95% CI 70%–82%) for lopinavir/ritonavir ($P=0.001$ between ritonavir-boosted PIs).

Regarding VF (on-treatment analysis), overall, 88% (581/664, 95% CI 85%–90%) of patients were virologically suppressed at the end of follow-up. In 14 patients (out of 83 with VF), PIMT was changed with only one detectable viral load. The probability of being free from VF after 12 months was 91.1% (453/497, 95% CI 88%–93%); 92.7% (293/316, 95% CI 89%–95%) for darunavir/ritonavir and 88.4% (160/181, 95% CI 83%–93%) for lopinavir/ritonavir ($P=0.139$ between ritonavir-boosted PIs). At VF, 30% ($n=25$) of patients had a viral load between 50 and 200 copies/mL, 31% ($n=26$) between 200 and 500 copies/mL and 39% ($n=32$) >500 copies/mL.

At month 24 of follow-up, time to TF was significantly shorter with lopinavir/ritonavir, but no differences were seen between the ritonavir-boosted PI combinations with regard to time to VF (Figure 2).

There was a significant gain in CD4 cell counts with both ritonavir-boosted PI combinations compared with baseline levels: 20 (−80–118) ($P=0.048$) and 33 (−66–159) ($P=0.001$) cells/mm^3 with darunavir/ritonavir and lopinavir/ritonavir, respectively, without significant differences between the drugs ($P=0.074$).

One hundred and fifty-one (23%) patients presented viral blips during follow-up. When adjusting for time of treatment, we observed 1.7 blips per 100 patients/month with darunavir/ritonavir and 1.9 blips per 100 patients/month with lopinavir/ritonavir ($P=$ not significant).

Tolerability and safety

A total of 158 patients stopped PIMT, 17% (75/435) treated with darunavir/ritonavir and 36% (83/229) receiving lopinavir/ritonavir; the reasons were VF in 73 (11%) (10 other patients continued PIMT despite VF), loss to follow-up in 11 (2%), adverse events in 40 (6%) (including 20 patients changing between PIMT), patient's decision in 8 (1%), death in 2 (0.3%) and other causes in 24 (4%) patients. The most frequently observed adverse events were gastrointestinal and metabolic side effects, with other toxicities occurring each in <1% of patients.

Interestingly, two patients presented CNS symptoms with lopinavir/ritonavir PIMT. One patient, with a nadir CD4 of 58 cells/mm^3 and prior failure to nelfinavir, but without resistance testing, a baseline CD4 of 1100 cells/mm^3 and 59 months of undetectable viral load prior to PIMT, had encephalitis with viral loads of 216 and 24 000 copies/mL in plasma and CSF, respectively. The other patient, with a nadir CD4 of 72 cells/mm^3, without prior failure to protease inhibitors, a baseline CD4 of 483 cells/mm^3 and 25 months of undetectable viral load prior to PIMT, had subacute cognitive impairment with undetectable viral load in plasma and low-level replication in CSF (435 copies/mL). Two other patients died, from unknown causes.

There were 20 patients who switched from one PIMT to another: 19 from lopinavir/ritonavir to darunavir/ritonavir due to gastrointestinal ($n=9$) or lipid disturbances ($n=10$) and one patient switched from darunavir/ritonavir to lopinavir/ritonavir due to a rash.

Predictors of VF and outcome following TF

By multivariate Cox regression analysis, CD4 nadir <200 cells/mm^3 and time with undetectable viral load prior to PIMT <24 months were independently associated with VF (Table 2). No association was found between VF and other covariates included in the model (HCV coinfection, prior VF with protease inhibitors, baseline CD4 <350 cells/mm^3 and ritonavir-boosted PI used).

Of the 158 patients who stopped PIMT, 24 (15%) did not have a subsequent antiretroviral therapy regimen (due to patient's decision, loss to follow-up or death). Of the remaining patients, 48 (30%) reintroduced the previous NRTI backbone, 13 (8%) changed to two NRTIs + another ritonavir-boosted PI, 14 (9%) switched to two NRTIs + non-NRTI, 6 (4%) changed to two NRTIs + an integrase inhibitor, 20 (13%) switched to the other PIMT, 3 (2%) received three NRTIs, 8 (5%) received a regimen with three new drugs (ritonavir-boosted PI, etravirine, integrase inhibitor or maraviroc) and a non-negligible 22 (14%) received dual therapy with a ritonavir-boosted PI plus a non-NRTI, an integrase inhibitor or maraviroc. Of these 158 patients, 16 (10%) did not resuppress viral replication after PIMT change, 68 (43%) reached undetectable viral load with the new treatment and we do not have follow-up information for the other 74 (47%). Only 17 patients (out of 83 showing VF) had resistance testing performed after VF. New resistance mutations in the protease were observed in three patients. In seven other patients, mutations were present in the protease (major RAM in one patient treated with

Table 1. Baseline characteristics

	Global (*n*=664)	DRV/r (*n*=435)	LPV/r (*n*=229)	*P*
Male	494 (74)	325 (75)	169 (74)	0.709
Age, years	46 (41–51)	46 (42–52)	45 (40–50)	0.064
HIV transmission route				0.459
IDU	228 (34)	144 (33)	84 (36)	
homosexual	206 (31)	138 (32)	68 (30)	
heterosexual	181 (27)	119 (27)	62 (27)	
haemophilia/transfusion	4 (1)	1 (1)	3 (1)	
other	45 (7)	32 (7)	13 (6)	
Nadir CD4, cells/mm^3	189 (76–297)	200 (81–312)	162 (74–261)	0.068
HCV positive	276 (42)	170 (39)	106 (46)	0.098
HIV infection, years	15 (9–19)	15 (10–20)	14 (8–19)	0.044
ART, years	11 (6–14)	12 (7–15)	9 (4–14)	0.004
Prior ART regimens	5 (2–7)	5 (3–7)	4 (2–6)	0.003
Protease inhibitor naive	68 (10)	36 (8)	32 (14)	0.031
Prior VF with protease inhibitor	226 (34)	143 (33)	83 (36)	0.438
Major protease inhibitor RAMs	44 (7)	25 (6)	19 (8)	0.043
Major DRV RAMs	2 (1)	1 (1)	1 (1)	0.505
Major LPV RAMs	9 (1)	6 (1)	3 (1)	0.726
HIV RNA <50 copies/mL prior to PIMT, months	49 (24–83)	55 (29–85)	42 (20–67)	<0.001
Baseline CD4, cells/mm^3	608 (432–806)	633 (457–819)	548 (384–780)	0.03
Reason for switch to PIMT				<0.001
adverse events	88 (28)	115 (27)	73 (32)	
simplification	426 (65)	300 (69)	126 (55)	
other	50 (7)	19 (4)	31 (13)	
TDF containing	392 (59)	262 (60)	130 (57)	
ABC containing	143 (22)	90 (21)	53 (23)	
ZDV, d4T, ddI	157 (24)	82 (19)	75 (33)	
Non-NRTI (EFV/NVP)	71 (11)	54 (12)	17 (7)	
RAL, ETR, MVC	67 (10)	61 (14)	6 (3)	
Same PI/r		161 (37)	185 (81)	
Other PI/r		219 (50)	25 (11)	
LPV		58 (13)	—	
DRV		—	1 (1)	
ATV		99 (23)	17 (7)	
FPV		34 (8)	4 (2)	
SQV		28 (6)	3 (1)	

Results are expressed as *n* (%) or median (IQR).
DRV/r, ritonavir-boosted darunavir; LPV/r, ritonavir-boosted lopinavir; IDU, intravenous drug user; ART, antiretroviral therapy; DRV, darunavir; LPV, lopinavir; TDF, tenofovir; ABC, abacavir; ZDV, zidovudine; d4T, stavudine; ddI, didanosine; EFV, efavirenz; NVP, nevirapine; RAL, raltegravir; ETR, etravirine; MVC, maraviroc; PI/r; protease inhibitor/ritonavir; ATV, atazanavir; FPV, fosamprenavir; SQV, saquinavir.

lopinavir/ritonavir), but we cannot know if these were new mutations as these patients had previously failed on a protease inhibitor-containing regimen and prior resistance testing was not available.

Discussion

In this cohort, 78% of patients receiving PIMT in the clinical setting remained free from TF after a median follow-up of 16 months. The effectiveness of PIMT in our study is higher than that reported from a French cohort[20] and consistent with efficacy data in randomized clinical trials.[10,11] Small differences in the PIMT outcome between clinical trials and our cohort are probably driven by patients' characteristics. Indeed, the risk of VF in our study, 12% after 16 months of PIMT, was similar to that observed in randomized clinical trials.[10–12,21]

When comparing the effectiveness of lopinavir/ritonavir versus darunavir/ritonavir, the TF rate was higher among patients receiving lopinavir/ritonavir. However, these differences must be taken cautiously as baseline characteristics were not comparable

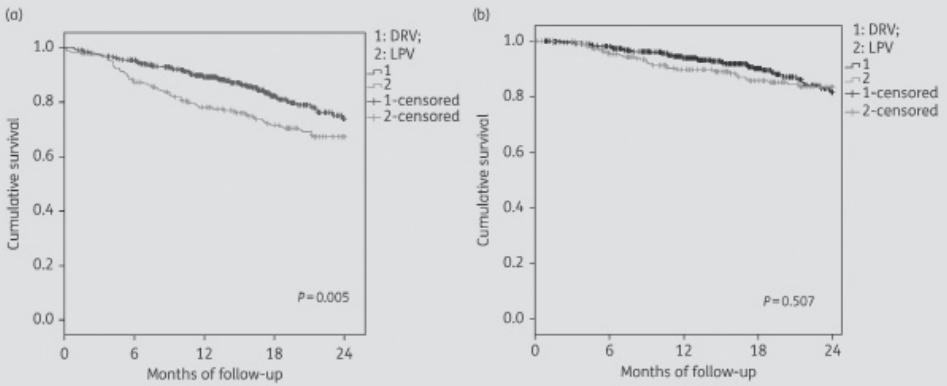

Figure 2. Outcomes of PIMT according to the ritonavir-boosted protease inhibitor used. Darunavir (DRV) is shown in black and lopinavir (LPV) in grey. (a) TF. (b) VF.

Table 2. Predictors of VF

	Univariate analysis[a] [HR (95% CI)]	Multivariate analysis[a] [HR (95% CI)]
Protease inhibitor/ritonavir used	1.03 (0.65–1.64), P=0.903	—
Time viral load <50 copies/mL prior to PIMT <12 months	1.26 (0.73–2.17), P=0.414	—
Time viral load <50 copies/mL prior to PIMT <24 months	1.80 (1.14–2.75), P=0.011	1.86 (1.20–2.91), P=0.006
CD4 nadir <200 cells/mm^3	1.48 (0.95–2.32), P=0.085	1.58 (1.01–2.49), P=0.048
HCV coinfection	1.02 (0.66–1.57), P=0.944	—
CD4 at PIMT initiation <350 cells/mm^3	1.32 (0.77–2.26), P=0.309	—
Prior VF with protease inhibitor/ritonavir	0.94 (0.60–1.46), P=0.768	—

[a]Cox proportional hazards regression model; HR, hazard ratio.

and no differences in terms of viral response were seen between both protease inhibitors. Similarly, differences between darunavir/ritonavir and lopinavir/ritonavir were not seen in the French cohort either, with both options being better than atazanavir/ritonavir PIMT.[20]

The strongest predictor of VF in our cohort was time on a suppressive viral regimen before PIMT switching. In agreement with previous studies, the risk of VF was almost 2-fold higher among patients with viral suppression <24 months previous to change.[20,22] Prolonged viral suppression might be a surrogate marker of lower viral reservoir size, which has been associated with a lower risk of VF with PIMT,[22] although it could also be a marker for better adherence to antiretroviral therapy. In addition, the risk of VF was 1.6-fold higher in patients with a CD4 nadir count <200 cells/mm^3. Consistent with these data, a trial evaluating PIMT with lopinavir/ritonavir was prematurely stopped because of a high rate of VF and the only predictor of failure was a low nadir CD4 cell count (<200 cells/mm^3).[23] Also, a nadir CD4 count <100 cells/mm^3 was a predictor of VF in another study with lopinavir/ritonavir.[24] Taken together, these data support guideline recommendations to avoid PIMT in patients with a low CD4 nadir.[9] In contrast with data from the MONET study,[10] in our cohort including 40% of patients infected with chronic hepatitis C, HCV coinfection was not associated with treatment outcome.

Remarkably, one-third of patients in our study had previously failed on a protease inhibitor-containing regimen, but the risk of VF was not increased in these patients, which highlights the high genetic barrier of both lopinavir/ritonavir and darunavir/ritonavir. Indeed, very few patients had new mutations in the protease after failing PIMT, confirming the difficulty of selecting mutations after failing on a ritonavir-boosted PI, as observed in clinical trials.[25,26] Conversely, in the French cohort, a trend for a higher probability of VF and TF was seen among the 9% of patients who had previously failed with protease inhibitors.[20] Notwithstanding this, our data do not support the use of PIMT in patients who have previously failed with protease inhibitors, even if no protease inhibitor-associated RAMs are present.

Regarding safety, adverse events leading to PIMT discontinuation were relatively rare. The most common side effects were

gastrointestinal and lipid disturbances, mainly with lopinavir/ritonavir. In 19 patients, PIMT was changed from lopinavir/ritonavir to darunavir/ritonavir for these reasons.

Consistent with data obtained in randomized clinical trials, almost one-quarter of patients receiving PIMT in our study had transient viraemia, with no differences in the incidence risk between both ritonavir-boosted PI combinations.[10,27,28] Low-level replication and transient elevations of viral load are frequently observed during PIMT, underscoring a lower antiviral potency of PIMT and less forgiveness for suboptimal adherence as compared with cART.[10,11] In fact, the main concern with PIMT is in regard to its efficacy to suppress viral replication in reservoirs, mainly in the CNS. In our cohort, two patients had evidence of CNS replication. In both cases the CD4 nadir was <100 cells/mm^3. In the French cohort also, with a slightly smaller sample size, two patients had HIV-related encephalopathy.[20] The MOST study with lopinavir/ritonavir PIMT was prematurely stopped due to an unexpected higher rate of VF both in blood and CSF, with CNS symptoms in four out of six patients failing therapy.[23] Another study showed increased astrocyte inflammatory markers with lopinavir/ritonavir PIMT[29] and there is a report of two cases of CSF breakthrough with darunavir/ritonavir PIMT,[30] although this is not exclusive to PIMT and has also been seen with triple therapy.[31] In another prospective trial, there was no greater cognitive decline or CSF viral escape in patients with PIMT compared with cART.[32] Thus, the actual risk of CNS escape among patients on PIMT is far from clear, but the incidence seems to be low.

Some limitations of our study must be pointed out. Its retrospective nature does not allow controlling for factors such as adherence and prevents us having information about replication in anatomic reservoirs, or fat or bone changes. This design does not allow the drawing of conclusions on the two main potential advantages of PIMT: avoiding long-term side effects of other drugs and cost reduction, which has fuelled PIMT use in Spain in the last few years and makes this strategy very appealing in areas with economic restrictions. Clinical trials have data for up to 48 months with lopinavir/ritonavir,[33] with an efficacy of 67% by ITT; with darunavir/ritonavir there are two trials, one with 24 month follow-up and an efficacy of 88%,[28] and another with 36 month follow-up and an efficacy of 69%.[34] However, differences in those trials when comparing monotherapy with standard triple therapy did not become larger. Further follow-up of our cohort will be necessary to confirm if our patients maintain effectiveness or similar decreases over time are seen. Finally, information from some patients after PIMT discontinuation is lacking, which can bias the results.

Despite these limitations, the results from our cohort, the largest reported to our knowledge, may be very useful as they describe the effectiveness of PIMT in routine practice, without the thorough control that takes place in trials, refine the risk of VF with PIMT and help clinicians to select the most suitable candidates. Although with a lower antiviral potency as compared with standard cART and concerns regarding ongoing viral replication in the CNS, PIMT might be an alternative strategy, mainly to avoid long-term toxicity and/or to save costs in the setting of economic restrictions.

In conclusion, almost 80% of patients receiving PIMT in our cohort remained free from TF after a median of 16 months of therapy and 88% remained free from VF. Sustained viral suppression >2 years prior to PIMT initiation and a nadir CD4 cell count >200 cells/mm^3 were independently associated with a favourable PIMT outcome.

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Author contributions

A. C. and M. C. conceived the study, participated in its design and coordination, participated in data analysis and drafted the manuscript. P. M., P. D., J. V., A. I., E. M., I. F., H. K., D. P., J. A. I. and M. P. recruited patients, carried out the study protocol and supervised data integrity and analysis. All the authors contributed to the final version of the manuscript.

References

1 Curran A, Ribera E. From old to new nucleoside reverse transcriptase inhibitors: changes in body fat composition, metabolic parameters and mitochondrial toxicity after the switch from thymidine analogs to tenofovir or abacavir. *Expert Opin Drug Saf* 2011; **10**: 389–406.

2 McComsey GA, Kitch D, Daar ES *et al*. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: AIDS Clinical Trials Group A5224s, a substudy of ACTG A5202. *J Infect Dis* 2011; **203**: 1791–801.

3 Stellbrink HJ, Orkin C, Arribas JR *et al*. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis* 2010; **51**: 963–72.

4 EACS. *Clinical Management and Treatment of HIV Infected Adults in Europe. Version 7.0. October 2013*. http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf (26 November 2013, date last accessed).

5 GeSIDA. *Documento de consenso de Gesida/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana (Actualización enero 2013)*. http://www.gesida-seimc.org/pcientifica/fuentes/DcyRc/gesidadcyrc2013-TAR-adulto.pdf (26 November 2013, date last accessed).

6 Ghosn J, Flandre P, Cohen-Codar I *et al*. Long-term (96-week) follow-up of antiretroviral-naive HIV-infected patients treated with first-line lopinavir/ritonavir monotherapy in the MONARK trial. *HIV Med* 2010; **11**: 137–42.

7 Gathe J, Yeh R, Mayberry C *et al*. Single agent therapy with lopinavir/ritonavir durably suppresses viral replication in ARV naïve patients: IMANI II - 96 week final results. In: *Abstracts of the Forty-sixth Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 2008*. Abstract H-1241. American Society for Microbiology, Washington, DC, USA.

8 Bunupuradah T, Chetchotisakd P, Ananworanich J *et al*. A randomized comparison of second-line lopinavir/ritonavir monotherapy versus tenofovir/lamivudine/lopinavir/ritonavir in patients failing NNRTI regimens: the HIV STAR study. *Antivir Ther* 2012; **17**: 1351–61.

9 Cameron DW, da Silva BA, Arribas JR *et al*. A 96-week comparison of lopinavir-ritonavir combination therapy followed by lopinavir-ritonavir monotherapy versus efavirenz combination therapy. *J Infect Dis* 2008; **198**: 234–40.

10 Arribas JR, Horban A, Gerstoft J *et al*. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/mL. *AIDS* 2010; **24**: 223–30.

11 Katlama C, Valantin MA, Algarte-Genin M *et al*. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. *AIDS* 2010; **24**: 2365–74.

12 Pulido F, Arribas JR, Delgado R *et al*. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and two nucleosides for maintenance therapy of HIV. *AIDS* 2008; **22**: F1–9.

13 Nunes EP, Santini de Oliveira M, Mercon M *et al*. Monotherapy with lopinavir/ritonavir as maintenance after HIV-1 viral suppression: results of a 96-week randomized, controlled, open-label, pilot trial (KalMo study). *HIV Clin Trials* 2009; **10**: 368–74.

14 Karlstrom O, Josephson F, Sonnerborg A. Early virologic rebound in a pilot trial of ritonavir-boosted atazanavir as maintenance monotherapy. *J Acquir Immune Defic Syndr* 2007; **44**: 417–22.

15 Wilkin TJ, McKinnon JE, DiRienzo AG *et al*. Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy: final 48-week clinical and virologic outcomes. *J Infect Dis* 2009; **199**: 866–71.

16 Ebrahim O, Hill A. Short-course induction with boosted saquinavir monotherapy for naive patients with late-stage infection. *AIDS* 2005; **19**: 211–2.

17 Kahlert C, Hupfer M, Wagels T *et al*. Ritonavir boosted indinavir treatment as a simplified maintenance 'mono'-therapy for HIV infection. *AIDS* 2004; **18**: 955–7.

18 Saumoy M, Tiraboschi J, Gutierrez M *et al*. Viral response in stable patients switching to fosamprenavir/ritonavir monotherapy (the FONT Study). *HIV Med* 2011; **12**: 438–41.

19 Johnson VA, Calvez V, Gunthard HF *et al*. Update of the drug resistance mutations in HIV-1: March 2013. *Top Antivir Med* 2013; **21**: 6–14.

20 Guiguet M, Ghosn J, Duvivier C *et al*. Boosted protease inhibitor monotherapy as a maintenance strategy: an observational study. *AIDS* 2012; **26**: 2345–50.

21 Clumeck N, Rieger A, Banhegyi D *et al*. 96 week results from the MONET trial: a randomized comparison of darunavir/ritonavir with versus without nucleoside analogues, for patients with HIV RNA <50 copies/mL at baseline. *J Antimicrob Chemother* 2011; **66**: 1878–85.

22 Lambert-Niclot S, Flandre P, Valantin MA *et al*. Factors associated with virological failure in HIV-1-infected patients receiving darunavir/ritonavir monotherapy. *J Infect Dis* 2011; **204**: 1211–6.

23 Gutmann C, Cusini A, Gunthard HF *et al*. Randomized controlled study demonstrating failure of LPV/r monotherapy in HIV: the role of compartment and CD4-nadir. *AIDS* 2010; **24**: 2347–54.

24 Pulido F, Perez-Valero I, Delgado R *et al*. Risk factors for loss of virological suppression in patients receiving lopinavir/ritonavir monotherapy for maintenance of HIV suppression. *Antivir Ther* 2009; **14**: 195–201.

25 Arribas JR, Delgado R, Arranz A *et al*. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and 2 nucleosides for maintenance therapy of HIV: 96-week analysis. *J Acquir Immune Defic Syndr* 2009; **51**: 147–52.

26 Lambert-Niclot S, Flandre P, Valantin MA *et al*. Resistant minority species are rarely observed in patients on darunavir/ritonavir monotherapy. *J Antimicrob Chemother* 2012; **67**: 1470–4.

27 Santos JR, Molto J, Llibre JM *et al*. Antiretroviral simplification with darunavir/ritonavir monotherapy in routine clinical practice: safety, effectiveness, and impact on lipid profile. *PLoS One* 2012; **7**: e37442.

28 Valantin MA, Lambert-Niclot S, Flandre P *et al*. Long-term efficacy of darunavir/ritonavir monotherapy in patients with HIV-1 viral suppression: week 96 results from the MONOI ANRS 136 study. *J Antimicrob Chemother* 2012; **67**: 691–5.

29 Du Pasquier RA, Jilek S, Kalubi M *et al*. Marked increase of the astrocytic marker S100B in the cerebrospinal fluid of HIV-infected patients on LPV/r-monotherapy. *AIDS* 2013; **27**: 203–10.

30 Gisslen M, Fuchs D, Hagberg L *et al*. Cerebrospinal fluid viral breakthrough in two HIV-infected subjects on darunavir/ritonavir monotherapy. *Scand J Infect Dis* 2012; **44**: 997–1000.

31 Canestri A, Lescure FX, Jaureguiberry S *et al*. Discordance between cerebral spinal fluid and plasma HIV replication in patients with neurological symptoms who are receiving suppressive antiretroviral therapy. *Clin Infect Dis* 2010; **50**: 773–8.

32 Perez-Valero I, Gonzalez-Baeza A, Estebanez M *et al*. Protease inhibitor mono-therapy is not associated with a higher rate or a different pattern of neurocognitive impairment than triple drug therapy. In: *Abstracts of the Twentieth Conference on Retroviruses and Opportunistic Infections, Atlanta, GA, 2013*. Abstract 406, p. 231. Foundation for Retrovirology and Human Health, Alexandria, VA, USA.

33 Pulido F, Delgado R, Perez-Valero I *et al*. Long-term (4 years) efficacy of lopinavir/ritonavir monotherapy for maintenance of HIV suppression. *J Antimicrob Chemother* 2008; **61**: 1359–61.

34 Arribas JR, Clumeck N, Nelson M *et al*. The MONET trial: week 144 analysis of the efficacy of darunavir/ritonavir (DRV/r) monotherapy versus DRV/r plus two nucleoside reverse transcriptase inhibitors, for patients with viral load <50 HIV-1 RNA copies/mL at baseline. *HIV Med* 2012; **13**: 398–405.

ARTICLE 2

Changes in cardiovascular biomarkers in HIV-infected patients switching from ritonavir-boosted protease inhibitors to raltegravir.

Esteban Martínez [a], Polyana M. d'Albuquerque [a,] Josep M. Llibre [b], Felix Gutierrez [c], Daniel Podzamczer [d], Antonio Antela [e], Juan Berenguer [f], Pere Domingo [g], Xabier Moreno [a], Ignacio Perez [a], Judit Pich [a], Jose´ M. Gatell [a], for the SPIRAL Trial Group.

[a]Hospital Clínic-IDIBAPS, Universitat de Barcelona, Barcelona; [b] Lluita contra la SIDA Foundation, Hospital Germans Trías i Pujol, Badalona; [c] Hospital Universitario de Elche, Universidad Miguel Hernández, Elche; [d] Hospital Universitari de Bellvitge, Universitat de Barcelona, L'Hospitalet de Llobregat; [e] Complexo Hospitalario Universitario de Santiago, Santiago de Compostela; [f] Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid; [g] Hospital de Sant Pau, Universitat Autònoma de Barcelona, Barcelona.

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Changes in cardiovascular biomarkers in HIV-infected patients switching from ritonavir-boosted protease inhibitors to raltegravir

Esteban Martínez[a], Polyana M. D'Albuquerque[a], Josep M. Llibre[b], Felix Gutierrez[c], Daniel Podzamczer[d], Antonio Antela[e], Juan Berenguer[f], Pere Domingo[g], Xabier Moreno[a], Ignacio Perez[a], Judit Pich[a], José M. Gatell[a], for the SPIRAL Trial Group

Background: Switching from boosted protease inhibitors (PI/r) to raltegravir (RAL) results in a better plasma lipid profile than continuing PI/r. Whether this strategy affects plasma biomarkers associated with atherosclerosis is unknown.

Methods: We assessed 48-week changes in fasting lipids and several biomarkers including serum high-sensitivity C-reactive protein (hsCRP), monocyte chemoattractant protein 1 (MCP-1), osteoprotegerin, interleukin (IL) 6, IL-10, tumor necrosis factor alpha (TNF-α), intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin and P-selectin, adiponectin, insulin, and D-dimer in otherwise healthy, virologically suppressed HIV-infected patients treated with PI/r who randomly switched from PI/r to RAL or continued with PI/r in the SPIRAL trial. Biomarkers and lipids at baseline and 48-week changes between both study arms were compared. Correlations between changes in biomarkers and changes in lipids were also evaluated.

Results: Of 273 patients initiating study drugs in the SPIRAL trial, 233 (119 RAL, 114 PI/r) remained on allocated therapy for 48 weeks and had sera available for the purpose of this substudy. Triglycerides (−28%, $P < 0.0001$), total (−14%, $P < 0.0001$), low-density lipoprotein (−9%, $P = 0.0069$), and high-density lipoprotein (−10%, $P = 0.0017$) cholesterol decreased in RAL relative to the PI/r group. Among biomarkers, hsCRP (−40%, $P < 0.0001$), MCP-1 (−20%, $P = 0.0003$), osteoprotegerin (−13%, $P = 0.0024$), IL-6 (−46%, $P < 0.0001$), TNF-α (−27%, $P = 0.0011$), insulin (−26%, $P < 0.0001$), and D-dimer (−8%, $P = 0.0187$) decreased in RAL relative to PI/r group, whereas IL-10 (+1%, $P = 0.7773$), ICAM-1 (−6%, $P = 0.1255$), VCAM-1(0%, $P = 0.8671$), E-selectin (−9%, $P = 0.2174$), P-selectin (−6%, $P = 0.3865$), and adiponectin (+8%, $P = 0.2028$) remained unchanged. Biomarkers and lipids changes at 48 weeks were weakly correlated.

Conclusion: Switching from PI/r to RAL induced significant changes in several cardiovascular biomarkers that were not completely explained by lipid changes.

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Keywords: cardiovascular biomarkers, protease inhibitors, raltegravir, switching

[a]Hospital Clínic-IDIBAPS, Universitat de Barcelona, Barcelona, [b]Lluita contra la SIDA Foundation, Hospital Germans Trías i Pujol, Badalona, [c]Hospital Universitario de Elche, Universidad Miguel Hernández, Elche, [d]Hospital Universitari de Bellvitge, Universitat de Barcelona, L'Hospitalet de Llobregat, [e]Complexo Hospitalario Universitario de Santiago, Santiago de Compostela, [f]Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, and [g]Hospital de Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain.

Correspondence to Esteban Martínez, Consultant & Associate Professor of Medicine, Infectious Diseases Unit, Hospital Clínic, University of Barcelona, 08036 Barcelona, Spain.

Tel: +34 93 227 55 74; fax: +34 93 451 44 38; e-mail: esteban@fundsoriano.es

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Introduction

Protease inhibitor-containing antiretroviral therapy has been associated with a higher incidence of myocardial infarction [1–4] and with an increased progression of subclinical atherosclerosis [5] relative to nonnucleoside reverse transcriptase inhibitor-containing antiretroviral therapy. In the D:A:D study [2], approximately one-third of the increased risk of myocardial infarction associated with protease inhibitor therapy was explained by metabolic abnormalities including plasma lipids. Although more recent protease inhibitors have shown less lipid impact than older ones, they require ritonavir boosting for optimal virological response. Ritonavir at doses similar to those used for protease inhibitor boosting has been shown to increase plasma lipids [6,7]. Mechanisms other than lipids including inflammation [8,9], endothelial dysfunction [10,11], insulin resistance [12], and macrophage accumulation of cholesterol [13,14] have been also suggested as contributing to the negative impact of ritonavir-boosted protease inhibitors on cardiovascular health. Some of these mechanisms are interrelated and the extent to which protease inhibitors affect them through lipid abnormalities is currently unclear.

Plasma biomarkers may help to assess mechanisms involved in the natural history of atherosclerosis [15]. In randomized clinical trials, plasma biomarkers have been used to support potential negative effects of uncontrolled HIV infection on the pathogenesis of cardiovascular disease [16,17] and their reversal upon initiation of antiretroviral therapy [18,19]. Most HIV-infected patients can expect achieving sustained suppression of viral replication in plasma with current antiretroviral therapy [20]. Despite sustained virological suppression, HIV-infected patients still show an accelerated rate of progression of subclinical atherosclerosis and increased plasma levels of inflammation and endothelial dysfunction biomarkers as compared with healthy controls [21]. Increases in plasma lipids are usually associated with increased inflammatory biomarkers in the general population [22], although this may not be necessarily the case in HIV-infected patients. Two independent randomized clinical trials in which nucleoside reverse transcriptase inhibitors were switched to either abacavir/lamivudine or tenofovir/emtricitabine in virologically suppressed HIV-infected patients did not show changes in cardiovascular biomarkers despite differences in lipid outcomes between arms [23,24].

Switching from protease inhibitors to abacavir, nevirapine or efavirenz, or raltegravir (RAL) in HIV-infected adults treated with sustained virological suppression has consistently resulted in better lipid profiles than continuing protease inhibitor therapy [25–27], thus indicating that protease inhibitor-induced lipid effects may be reversible at least in part. Whether improvement in plasma lipids by switching protease inhibitors will be accompanied by improvement in cardiovascular biomarkers is unclear. We aimed to assess whether switching from ritonavir-boosted protease inhibitors to RAL in HIV-infected adults with sustained virological suppression in plasma induced significant changes in cardiovascular biomarkers. Secondarily, we aimed to know whether there was any association between changes in plasma lipids and changes in cardiovascular biomarkers.

Methods

Patients

The SPIRAL trial enrolled otherwise clinically stable HIV-1-infected patients aged 18 years or older who were receiving combination antiretroviral therapy consisting of at least two antiretroviral agents other than a protease inhibitor and a ritonavir-boosted protease inhibitor including indinavir, fosamprenavir, saquinavir, lopinavir, atazanavir, tipranavir, or darunavir and showing plasma HIV-1 RNA below 50 copies/ml for at least the previous 6 months. The main study had a primary endpoint consisting of proportion of patients free of treatment failure at 48 weeks ('noncompleter = failure' intent-to-treat analysis) and secondary endpoints including proportion of patients free of virological failure, time to treatment or virological failure, changes in CD4 and CD8 cell counts and in fasting plasma lipids, and incidence of adverse events. These results have been reported elsewhere [27]. In addition to the cardiovascular biomarkers substudy reported here, other substudies have focused on intensive lipid [28] and body composition [29] outcomes. Briefly, patients were randomized to switch from the ritonavir-boosted protease inhibitor to RAL or to continue on the ritonavir-boosted protease inhibitor while maintaining the same background therapy. Twenty (14%) patients in each group had discontinued study drugs before 48 weeks or had no paired serum samples at baseline and at 48 weeks. One patient assigned to RAL progressed to AIDS, but no patient developed cardiovascular events or died. Institutional Review Board approval and informed consent were obtained on all participants.

Laboratory parameters

We aimed to investigate several mechanisms associated with atherogenesis including inflammation, endothelial dysfunction, insulin resistance, and hypercoagulability [30,31]. Following our experience with cardiovascular biomarkers in a previous study [23], we planned to assess markers associated with inflammation including high-sensitivity C-reactive protein (hsCRP), monocyte chemoattractant protein 1 (MCP-1), osteoprotegerin (OPG), interleukin 6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor alpha (TNF-α); markers associated with endothelial dysfunction including intercellular adhesion

molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), E-selectin, and P-selectin; markers associated with insulin resistance including adiponectin and insulin; and D-dimer as a marker associated with hypercoagulability. Some of these markers are known to be involved in more than one mechanism [30,31]. Total and high-density lipoprotein (HDL) cholesterol and triglycerides were measured using commercial enzymatic colorimetric kits at each site throughout follow-up. Low-density lipoprotein (LDL) cholesterol was measured indirectly whenever triglycerides were lower than 400 mg/dl; otherwise, it was measured directly.

EDTA and sodium citrate plasma (Vacutainer System; Beckton Dickinson, San Jose, California, USA) samples collected after at least 8-h overnight fast at baseline and at 48 weeks were stored at −80°C at each of the participating centers until central measurement of cardiovascular biomarkers. Cardiovascular markers were measured by experienced technicians blinded to treatment and data were codified to ensure blind statistical analyses. hsCRP was determined by particle-enhanced immunonephelometry (Dade Behring, Marburg, Germany). MCP-1 (Quantikine, Human CCL2/MCP-1 Immunoassay), OPG (DuoSet ELISA Development System, Human OPG/TNFRSF11B), IL-6 (Quantikine HS, Human IL-6 Immunoassay), IL-10 (Quantikine HS, Human IL-10 Immunoassay), TNF-α (Quantikine HS, Human TNF-α Immunoassay), ICAM-1, VCAM-1, E-selectin, and P-selectin (Fluorokine MAP, Human Adhesion Molecule MultiAnalyte Profiling Base Kit) were measured using commercially available ELISA assays (R&D Systems, Minneapolis, Minnesota, USA). Adiponectin was measured by radioimmunoassay (Linco Research, St. Charles, Missouri, USA). Insulin was measured by a monoclonal immunoradiometric assay (Medgenix Diagnostics, Fleunes, Belgium). D-dimer was quantitatively measured from sodium citrate plasma samples using a commercially available latex-enhanced turbidimetric test (Dade Behring, Marburg, Germany). Intra-assay coefficients of variation for laboratory markers measured were hsCRP 3.1%, MCP-1 4.9–7.8%, OPG 4–10%, IL-6 1.6–4.2%, IL-10 1.7–5.0%, TNF-α 4.2–5.2%, ICAM-1 3.6–5.2%, VCAM-1 2.3–3.6%, E-selectin 5.2–6.6%, P-selectin 4.9–5.6%, adiponectin 3.8%, insulin 5.2%, and D-dimer 1.3–3.0%. Inter-assay coefficients of variation for laboratory markers were hsCRP 2.5%, MCP-1 4.6–6.7%, OPG 7.0–8.0%, IL-6 3.3–6.4%, IL-10 5.9–7.5%, TNF-α 4.6–7.4%, ICAM-1 4.4–6.8%, VCAM-1 5.5–7.8%, E-selectin 7.3–8.7%, P-selectin 7.9–9.9%, adiponectin 5.5%, insulin 6.9%, and D-dimer 0.8–3.8%. The lowest limits of detection for laboratory markers were hsCRP 0.01 mg/dl, MCP-1 5.0 pg/ml, OPG 62.5 pg/ml, IL-6 0.039 pg/ml, IL-10 0.5 pg/ml, TNF-α 0.106 pg/ml, ICAM-1 96 pg/ml, VCAM-1 600 pg/ml, E-selectin 9 pg/ml, P-selectin 500 pg/ml, adiponectin 1.5 ng/ml, insulin 1 mU/l, and D-dimer 0.17 mg/l.

Interpretation of the results

Samples disclosing undetectable levels of any marker were retested for confirmation. For patients with confirmed measurements of laboratory markers below the limit of quantification, we assumed the respective lower limit of quantification for data analyses. At least one of the markers should show a statistical difference in the change from baseline to 48 weeks between arms to consider that the mechanism associated with that marker was potentially caused by any of study drugs.

Statistical analyses

Biomarkers and lipids at baseline and 48-week changes between patients assigned to either RAL or ritonavir-boosted protease inhibitor were compared using the Wilcoxon rank sum test. Changes in biomarkers and lipids were assessed both as absolute and percentage changes relative to baseline. Variability in absolute changes was higher in those with higher baseline values. The model assumption of homoscedasticity was better met when evaluating percentage changes. Therefore, results on the percentage scale were more reliable and are reported here. The punctual estimation and 95% confidence interval of difference in medians was estimated with the methodology of Hodges–Lehman using the distribution free of Moses. Correlations between continuous variables were evaluated using Spearman's rank correlation test. Because lopinavir and atazanavir were the most common protease inhibitors used in the SPIRAL study, additional analyses comparing 48-week changes in lipids and biomarkers between patients who were receiving either lopinavir or atazanavir at baseline were performed. Statistical analyses were carried out using Stata 9.2 (StataCorp LP, College Station, Texas, USA) and StatXact 6 (Cytel Inc., Cambridge, Massachusetts, USA). The sponsors of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The SPIRAL trial is registered with ClinicalTrials.gov number NCT00528892.

Results

Population

Between 4 April and 31 December 2008, 339 patients were assessed for eligibility, 282 underwent randomization and 273 (RAL, $n = 139$; ritonavir-boosted protease inhibitor, $n = 134$) received at least one dose of study drugs. Two hundred and thirty-three patients (RAL, $n = 119$; ritonavir-boosted protease inhibitor, $n = 114$) remained on their allocated therapy for 48 weeks and had paired sera at baseline and at 48 weeks available. None of them had experienced virological failure throughout the SPIRAL study follow-up. Baseline characteristics are

shown in Table 1. Baseline characteristics of patients not included in the biomarker substudy were similar to those of patients included. Most of the patients (76%) were men and median CD4 cell count was 516 cells/μl. Most common protease inhibitors at entry were lopinavir ($n=106$, 45%) and atazanavir ($n=85$, 36%). Eighty-six (37%) patients had received prior suboptimal therapy with one or two nucleoside reverse transcriptase inhibitors exclusively, but all of them had this therapy prescribed before 1997. Although 85 (36%) patients had experienced prior virological failure, HIV-1 RNA in the population included had been maintained below detection level for a median (interquartile range) of 71 (42–104) months before randomization.

Laboratory markers

The values of laboratory markers at baseline and 48-week changes are shown in Table 2. Markers both at baseline and at 48 weeks were detectable in at least 80% of the patients, except for D-dimer that was detected in only 50% of the patients. Because biomarkers values may be extremely high in the presence of an acute inflammatory process, we looked into maximum biomarkers values and no outliers were found. For instance, maximum detectable hsCRP at baseline and at 48 weeks were 2.63 and 1.28 mg/dl in the RAL arm and 1.79 and 1.83 mg/dl in the ritonavir-boosted protease inhibitor arm.

The median difference of percentage change RAL minus ritonavir-boosted protease inhibitor (95% confidence interval) is shown in Fig. 1a. There were significant decreases in hsCRP (−40%, $P<0.0001$), MCP-1 (−20%, $P=0.0003$), OPG (−13%, $P=0.0024$), IL-6 (−46%, $P<0.0001$), TNF-α (−27%, $P=0.0011$), insulin (−26%, $P<0.0001$), and D-dimer (−8%, $P=0.0187$) in the RAL group relative to the PI/r group, whereas IL-10 (+1%, $P=0.7773$), ICAM-1 (−6%, $P=0.1255$), VCAM-1 (0%, $P=0.7704$), E-selectin (−9%, $P=0.2174$), P-selectin (−6%, $P=0.3865$), and adiponectin (+8%, $P=0.2028$) remained unchanged.

Lipids

Fasting plasma lipids at baseline and at 48 weeks are shown in Table 3, and 48-week percentage changes in plasma lipids and median differences of percentage changes RAL minus ritonavir-boosted protease inhibitor are shown in Fig. 1b. Although there were no differences in any lipid parameter at baseline, triglycerides (−28%, $P<0.0001$), total (−14%, $P<0.0001$), LDL (−9%, $P=0.0069$), and HDL (−10%, $P=0.0017$) cholesterol significantly decreased in RAL group relative to ritonavir-boosted protease inhibitor group, whereas total-to-HDL cholesterol ratio remained unchanged (−5%, $P=0.1000$).

Correlations between markers and lipids

Correlations between markers and/or lipids at baseline are shown in Table 4. At baseline, significant correlations between markers reflecting similar mechanisms were found. Correlations were particularly strong among baseline markers associated with endothelial dysfunction

Table 1. Baseline characteristics.

	Raltegravir ($n=119$)	PI/r ($n=114$)
Age [years, median (IQR)]	43 (40–49)	44 (40–50)
Male sex [*n* (%)]	94 (79)	83 (73)
Antiretroviral backbone at entry [*n* (%)]		
3TC/FTC + TDF	69 (58)	64 (56)
3TC/FTC + ABC	24 (20)	23 (20)
3TC/FTC + ZDV	9 (8)	10 (9)
Other	17 (14)	17 (15)
PI/r at entry [*n* (%)]		
LPV/r	52 (44)	54 (47)
ATV/r	45 (38)	40 (35)
Other	22 (18)	20 (18)
Patients on their first antiretroviral regimen [*n* (%)]	15 (13)	14 (12)
Exposure to antiretroviral therapy [years, median (range)]	10 (5–12)	10 (6–12)
Exposure to protease inhibitor-based therapy [months, median (range)]	31 (19–45)	30 (17–50)
Patients with previous suboptimal antiretroviral therapy[a] or virological failure [*n* (%)]	68 (55)	55 (48)
Patients with AIDS [*n* (%)]	43 (36)	42 (37)
CD4 cell count [cells/μl, median (IQR)]	518 (368–766)	512 (371–730)
CD8 cell count [cells/μl, median (IQR)]	824 (633–1027)	807 (616–1088)
Triglycerides >200 mg/dl [*n* (%)]	48 (40)	44 (39)
Total cholesterol >240 mg/dl [*n* (%)]	18 (15)	17 (15)
LDL cholesterol >160 mg/dl [*n* (%)]	16 (13)	15 (13)
HDL cholesterol <40 mg/dl [*n* (%)]	45 (38)	38 (33)
Lipid-lowering therapy [*n* (%)]	23 (19)	23 (20)
Any abnormal lipid or lipid-lowering therapy [*n* (%)]	76 (64)	70 (62)

3TC, lamivudine; ABC, abacavir; ATV/r, ritonavir-boosted atazanavir; FTC, emtricitabine; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; LPV/r, ritonavir-boosted lopinavir; PI/r, ritonavir-boosted protease inhibitor; TDF, tenofovir; ZDV, zidovudine.
[a]Antiretroviral therapy containing one or two nucleoside reverse transcriptase inhibitors exclusively.

Table 2. Laboratory markers at baseline and 48-week percentage change in participants assigned to raltegravir or ritonavir-boosted protease inhibitor.

	Raltegravir ($n=119$)				PI/r ($n=114$)					
Laboratory marker	Baseline [median (IQR)]	Number (%) of patients with detectable measurement at baseline	48-week percentage change [median (IQR)]	Number (%) of patients with detectable measurement at 48 weeks	Baseline [median (IQR)]	Number (%) of patients with detectable measurement at baseline	48-week percentage change [median (IQR)]	Number (%) of patients with detectable measurement at 48 weeks	*P* value for comparisons between baseline values	*P* value for comparisons between 48-week percentage change values
hsCRP (mg/dl)	0.16 (0.04–0.50)	105 (88)	−50.00 (−76.25 to 0.00)	90 (76)	0.13 (0.05–0.49)	99 (87)	0.00 (−33.58 to 33.33)	106 (93)	0.7500	<0.0001
MCP-1 (pg/ml)	219 (173–300)	119 (100)	−10.02 (−84.96 to 27.64)	119 (100)	243 (176–312)	114 (100)	26.64 (−31.21 to 89.35)	114 (100)	0.4566	0.0002
OPG (pg/ml)	1243 (848–1613)	119 (100)	−15.33 (−24.12 to 4.51)	119 (100)	1175 (857–1465)	114 (100)	3.95 (−18.31 to 21.22)	113 (99)	0.5782	0.0024
IL-6 (pg/ml)	2.69 (1.57–5.62)	109 (92)	−31.12 (−53.00 to 0.00)	106 (89)	2.82 (0.60–5.26)	96 (84)	5.17 (−23.78 to 71.25)	99 (87)	0.3782	<0.0001
IL-10 (pg/ml)	50.99 (39.87–58.72)	108 (91)	0.12 (−11.03 to 11.88)	118 (99)	50.02 (40.88–59.80)	113 (99)	−0.10 (−9.11 to 8.41)	113 (99)	0.7308	0.7773
TNF-α (pg/ml)	6.29 (3.44–11.73)	116 (97)	−27.00 (−49.16 to 1.63)	113 (95)	6.45 (4.23–9.54)	114 (100)	3.07 (−31.01 to 38.66)	113 (99)	0.9902	0.0011
ICAM-1 (pg/ml)	321 340 (250 052–397 325)	105 (88)	−2.68 (−19.41 to 7.84)	105 (88)	352 452 (198 566–438 157)	95 (83)	4.00 (−15.67 to 20.94)	93 (82)	0.7366	0.1255
VCAM-1 (pg/ml)	775 538 (557 895–900 457)	101 (85)	0.00 (−13.96 to 15.34)	102 (86)	801 530 (551 270–997 728)	91 (80)	0.00 (−16.48 to 13.21)	87 (76)	0.7704	0.8671
Selectin E (pg/ml)	31 636 (16 641–41 455)	100 (84)	−8.01 (−36.79 to 25.30)	104 (87)	26 742 (14 713–38 277)	91 (80)	0.00 (−21.12 to 30.64)	91 (80)	0.4104	0.2174
Selectin P (pg/ml)	63 877 (33 347–89 355)	99 (83)	−1.22 (−34.76 to 36.39)	104 (87)	49 456 (29 888–78 924)	90 (79)	0.00 (−22.29 to 37.07)	90 (79)	0.3784	0.3865
Adiponectin (ng/ml)	7.90 (4.50–11.00)	119 (100)	15.48 (−14.74 to 45.53)	118 (99)	7.10 (4.90–10.00)	113 (99)	5.80 (−17.42 to 35.90)	113 (99)	0.7617	0.2028
Insulin (mU/l)	12.70 (8.20–18.10)	119 (100)	−19.83 (−39.39 to −1.69)	119 (100)	12.60 (6.50–16.50)	114 (100)	5.57 (−16.35 to 27.27)	114 (100)	0.4873	<0.0001
D-dimer (mg/l)	0.18 (0.17–0.27)	61 (51)	0.00 (−31.91 to 5.88)	56 (47)	0.19 (0.17–0.32)	63 (55)	0.00 (−6.90 to 13.16)	63 (55)	0.4634	0.0187

hsCRP, high sensitivity C-reactive protein; ICAM, intercellular adhesion molecule; IL, interleukin; MCP, monocyte chemoattractant protein; OPG, osteoprotegerin; PI/r, ritonavir-boosted protease inhibitor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

and insulin resistance. We also found that baseline plasma lipids correlated well with each other. There were significant correlations between insulin, adiponectin, or D-dimer and several plasma lipids at baseline. In addition, there were significant, albeit small, correlations between IL-6 or P-selectin and total cholesterol. All these correlations were no longer significant when multiplicity was accounted for. In general, baseline markers of inflammation or endothelial dysfunction did not correlate with baseline plasma lipids.

Correlations between changes in markers and/or lipids at 48 weeks are shown in Table 5. We found that 48-week changes in biomarkers reflecting similar mechanisms correlated well with each other. Similarly, 48-week changes in lipids also correlated well between them. There were significant though not strong correlations between changes in a few markers (hsCRP, MCP-1, and insulin) and changes in some lipids (triglycerides, total cholesterol, or LDL cholesterol).

Impact of baseline lopinavir vs. atazanavir on lipid and biomarker changes

Lipid and biomarker changes in patients switching from either lopinavir or atazanavir in the RAL arm or continuing with either lopinavir or atazanavir in the ritonavir/boosted protease inhibitor arm are shown in Fig. 2a and b, respectively. Data in the figures are restricted to lipids and biomarkers that had shown significant 48-week changes between treatment arms.

In patients switching to RAL, triglycerides decreased significantly more when the protease inhibitor discontinued was lopinavir (median −50%, 95% confidence interval −59 to −9) than when it was atazanavir (median −24%, 95% confidence interval −42 to −1%) (median difference of percentage change in triglycerides atazanavir minus lopinavir 19, 95% confidence interval 5–33, $P=0.0097$). Similarly, total cholesterol decreased significantly more when the protease inhibitor discontinued was lopinavir (median −15%, 95% confidence interval −22 to −7%) than when it was atazanavir (median −7%, 95% confidence interval −12 to 4%) (median difference of percentage change in total cholesterol atazanavir minus lopinavir 8, 95% confidence interval 2–14, $P=0.0189$). There were no differences between lopinavir and atazanavir in other lipids than triglycerides or total cholesterol in patients switching to RAL and in no lipid parameter in patients continuing protease inhibitors (data not shown).

Although biomarkers from patients switching from lopinavir to RAL decreased more than biomarkers from patients switching from atazanavir to RAL, differences were only significant for OPG (Fig. 2b). Median (95% confidence interval) atazanavir minus lopinavir difference of percentage changes were hsCRP 10 (−10 to 39), $P=0.3362$; MCP-1 2 (−14 to 18), $P=0.7175$; OPG 12

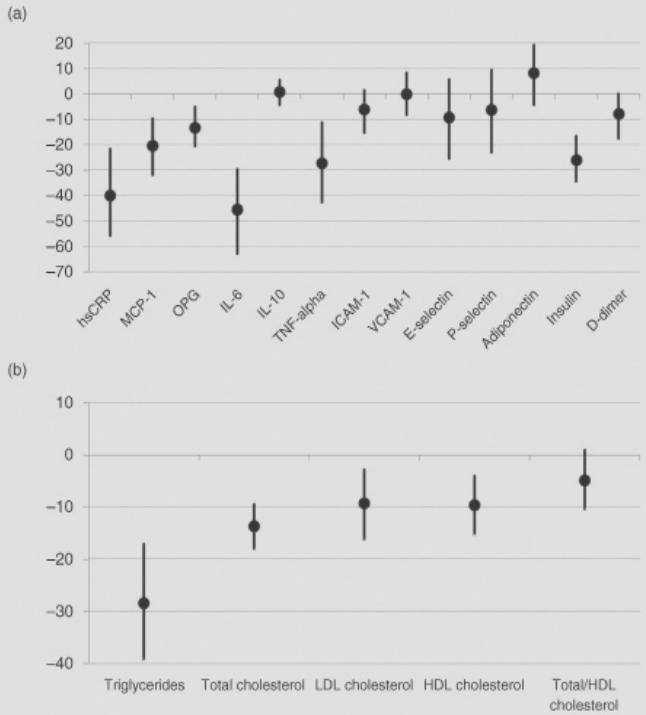

Fig. 1. Median difference of percentage change in biomarkers and lipids. (a) Median difference of percentage change in biomarkers raltegravir minus ritonavir-boosted protease inhibitor (95% confidence interval). (b) Median difference of percentage change in lipids raltegravir minus ritonavir-boosted protease inhibitor (95% confidence interval). HDL, high-density lipoprotein; LDL, low-density lipoprotein.

(3–24), $P=0.0134$; IL-6 11 (−8 to 26), $P=0.2660$; TNF-α 14 (−10 to 34), $P=0.2350$; insulin 7 (−6 to 17), $P=0.2513$; and D-dimer 7 (−3 to 26), $P=0.1891$. There were no differences between lopinavir and atazanavir in any biomarker in patients continuing protease inhibitors (data not shown).

Discussion

Although dyslipidemia was not required among inclusion criteria in SPIRAL trial [27], more than 60% of patients had abnormal plasma lipid values or were taking lipid-lowering therapy at baseline. Baseline values of

Table 3. Fasting plasma lipids at baseline and 48-week percentage change in participants assigned to raltegravir or ritonavir-boosted protease inhibitor.

	Raltegravir ($n=119$)		PI/r ($n=114$)			
Plasma lipids	Baseline [median (IQR)]	48-week percentage change [median (IQR)]	Baseline [median (IQR)]	48-week percentage change [median (IQR)]	*P* value for comparisons between baseline values	*P* value for comparisons between 48-week percentage change values
Triglycerides (mg/dl)	163 (118–255)	−33.62 (−55.07 to −4.88)	184 (115–247)	−7.95 (−25.89 to 23.18)	0.9217	<0.0001
Total cholesterol (mg/dl)	198 (173–224)	−11.73 (−23.02 to −3.45)	195 (168–222)	1.67 (−8.18 to 10.26)	0.6837	<0.0001
LDL cholesterol (mg/dl)	126 (100–144)	−9.79 (−23.73 to 2.00)	130 (100–154)	−2.20 (13.40 to 13.78)	0.5624	0.0069
HDL cholesterol (mg/dl)	45 (35–55)	−4.63 (−14.88 to 8.74)	42 (35–50)	3.85 (−6.73 to 19.85)	0.1739	0.0017
Total-to-HDL cholesterol ratio	4.43 (3.65–5.68)	−10.65 (−22.51 to 1.58)	4.90 (3.99–5.65)	−4.78 (−15.62 to 6.17)	0.1000	0.1000

HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; PI/r, ritonavir-boosted protease inhibitor.

Table 4. Correlations between markers and/or lipids at baseline.

	Total cholesterol	LDL cholesterol	HDL cholesterol	hsCRP	MCP-1	OPG	IL-6	IL-10	TNF-α	ICAM-1	VCAM-1	E-selectin	P-selectin	Adiponectin	Insulin	D-dimer
Triglycerides	0.1682 ($P = 0.022$)		−0.4346 ($P < 0.0001$)			0.1274 ($P = 0.0840$)								−0.4282 ($P < 0.0001$)	0.3839 ($P < 0.0001$)	
Total cholesterol	–	0.8832 ($P < 0.0001$)	0.3825 ($P < 0.0001$)				0.1835 ($P = 0.0124$)						0.1564 ($P = 0.0335$)			0.1969 ($P = 0.0072$)
LDL cholesterol	–	–	0.2925 ($P = 0.0002$)				0.1380 ($P = 0.0809$)						0.1564 ($P = 0.0558$)	0.1552 ($P = 0.0494$)		0.2128 ($P = 0.0067$)
HDL cholesterol	–	–	–		−0.1455 ($P = 0.0547$)									0.4032 ($P < 0.0001$)	−0.2410 ($P = 0.0012$)	−0.1899 ($P = 0.0114$)
hsCRP	–	–	–	–											0.2484 ($P = 0.0007$)	
MCP-1	–	–	–	–	–		0.1775 ($P = 0.0162$)	−0.1609 ($P = 0.030$)								
OPG	–	–	–	–	–	–	–	−0.2591 ($P = 0.0004$)					−0.1889 ($P = 0.0100$)			
IL-6	–	–	–	–	–	–	–	–					−0.2109 ($P = 0.0040$)			
IL-10	–	–	–	–	–	–	–	–								
TNF-α	–	–	–	–	–	–	–	–	–		0.7071 ($P < 0.0001$)	0.6417 ($P < 0.0001$)	0.4354 ($P < 0.0001$)			
ICAM-1	–	–	–	–	–	–	–	–	–	–	–	0.6722 ($P < 0.0001$)	0.5793 ($P < 0.0001$)			
VCAM-1	–	–	–	–	–	–	–	–	–	–	–	–	0.6079 ($P < 0.0001$)			
E-selectin	–	–	–	–	–	–	–	–	–	–	–	–	–	−0.1341 ($P = 0.0689$)		
P-selectin	–	–	–	–	–	–	–	–	–	–	–	–	–	–	−0.4164 ($P < 0.0001$)	
Adiponectin	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0.2097 ($P = 0.0042$)
Insulin	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	

Data are expressed as Spearman's rho (*P* value). Data reported are restricted to those correlations showing a *P* value <0.10. HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; ICAM, intercellular adhesion molecule; IL, interleukin; LDL, low-density lipoprotein; MCP, monocyte chemoattractant protein; OPG, osteoprotegerin; PI/r, ritonavir-boosted protease inhibitor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

Table 5. Correlations between 48-week changes in markers and/or lipids.

	Total cholesterol	LDL cholesterol	HDL cholesterol	hsCRP	MCP-1	OPG	IL-6	IL-10	TNF-α	ICAM-1	VCAM-1	E-selectin	P-selectin	Adiponectin	Insulin	D-dimer
Triglycerides	0.5107 ($P < 0.0001$)		−0.1494 ($P = 0.0532$)				0.1324 ($P = 0.0748$)	−0.1246 ($P = 0.0939$)							0.2842 ($P = 0.0001$)	
Total cholesterol	–	0.7801 ($P < 0.0001$)	0.3943 ($P < 0.0001$)	0.2415 ($P = 0.0016$)	0.1608 ($P = 0.0320$)	0.1268 ($P = 0.0881$)									−0.2125 ($P = 0.0040$)	
LDL cholesterol	–	–	0.3339 ($P < 0.0001$)	0.1362 ($P = 0.0965$)	0.1807 ($P = 0.0202$)											
HDL cholesterol	–	–	–									−0.1342 ($P = 0.0847$)	−0.1295 ($P = 0.0953$)			
hsCRP	–	–	–	–	0.3045 ($P < 0.0001$)		0.2656 ($P = 0.0003$)								0.1694 ($P = 0.0212$)	
MCP-1	–	–	–	–	–	0.1907 ($P = 0.0101$)	0.3076 ($P < 0.0001$)								0.2101 ($P = 0–0045$)	
OPG	–	–	–	–	–	–	0.2015 ($P = 0–0060$)									
IL-6	–	–	–	–	–	–	–					0.1374 ($P = 0.0637$)			0.2146 ($P = 0.0033$)	
IL-10	–	–	–	–	–	–	–	–								
TNF-α	–	–	–	–	–	–	–	–	–							
ICAM-1	–	–	–	–	–	–	–	–	–	–	0.8080 ($P < 0.0001$)	0.8030 ($P < 0.0001$)	0.6742 ($P < 0.0001$)		0.1275 ($P = 0.0838$)	
VCAM-1	–	–	–	–	–	–	–	–	–	–	–	0.7574 ($P < 0.0001$)	0.6933 ($P < 0.0001$)	−0.2254 ($P = 0.0021$)		
E-selectin	–	–	–	–	–	–	–	–	–	–	–	–	0.7804 ($P < 0.0001$)	0–0.1272 ($P = 0.087$)		
P-selectin	–	–	–	–	–	–	–	–	–	–	–	–	–	–	−0.1263 ($P = 0.0876$)	−0.1228 ($P = 0804$)
Adiponectin	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	
Insulin	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	

Data are expressed as Spearman's rho (P value). Data reported are restricted to those correlations showing a P value <0.10. HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; ICAM, intercellular adhesion molecule; IL, interleukin; LDL, low-density lipoprotein; MCP, monocyte chemoattractant protein; OPG, osteoprotegerin; PI/r, ritonavir-boosted protease inhibitor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule.

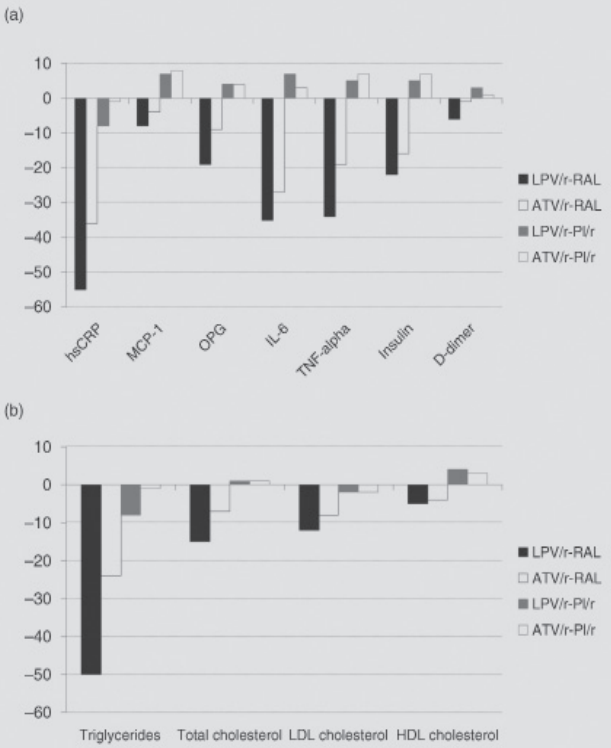

Fig. 2. Changes in biomarkers and lipids in patients receiving either lopinavir or atazanavir. (a) The 48-week changes in biomarkers between patients who were receiving either lopinavir (LPV/r) or atazanavir (ATV/r) at baseline in each treatment group. (b) The 48-week changes in lipids between patients who were receiving either lopinavir (LPV/r) or atazanavir (ATV/r) at baseline in each treatment group. HDL, high-density lipoprotein; LDL, low-density lipoprotein; PI/r, ritonavir-boosted protease inhibitor; RAL, raltegravir.

biomarkers such as hsCRP, IL-6, or D-dimer were not substantially different from those reported in SMART study participants, who had an HIV RNA level 400 copies/ml or less at baseline [32], although in that study patients receiving a nonnucleoside reverse transcriptase inhibitor had higher levels of hsCRP than patients receiving a protease inhibitor.

Switching from ritonavir-boosted protease inhibitors to RAL in the SPIRAL trial led not only to significant changes in plasma lipids but also to significant changes in several cardiovascular biomarkers associated with inflammation, insulin resistance, and hypercoagulability, although not in those associated with endothelial dysfunction. As a marker of quality, we found significant correlations at baseline between markers that measure similar mechanisms, between plasma lipids, and between insulin, adiponectin, or D-dimer and several plasma lipids. Although 48-week changes in lipids were correlated between them, and 48-week changes in biomarkers reflecting similar mechanisms were also well correlated between them, there were few and not strong significant correlations between changes in lipids and changes in biomarkers suggesting that decreases in inflammation, insulin resistance, and hypercoagulability biomarkers in patients switching from ritonavir-boosted protease inhibitors to RAL in SPIRAL trial were rather independent of lipid changes.

Changes in biomarkers and lipids in patients switching from ritonavir-boosted protease inhibitors to RAL in SPIRAL trial could be theoretically due to discontinuation of protease inhibitors, introduction of RAL, or both. In contrast to protease inhibitors, there are no data linking RAL use to cardiovascular disease, subclinical atherosclerosis, inflammation, endothelial dysfunction, or hypercoagulability. RAL has shown almost neutral lipid effect in antiretroviral-naive patients [33] and a better lipid and insulin resistance profile than that of lopinavir/ritonavir in healthy volunteers [34,35]. Interestingly,

2-week RAL therapy was associated with significantly lower plasma hsCRP than 2-week lopinavir/ritonavir therapy in an open-label, cross-over randomized study in HIV-negative healthy men [36]. A recent randomized study also reported significant decreases in hsCRP, IL-6, and D-dimer at 24 weeks in virologically suppressed patients switching from enfuvirtide to RAL [37]. Another study measured markers of immune activation, microbial translocation, and T-cell exhaustion in 15 treatment-naive patients initiating RAL-containing therapy and compared results with historical controls who had received a similar duration of non-RAL therapy and to HIV-uninfected controls [38]; at 24 weeks, levels of immune activation, microbial translocation, and T-cell exhaustion were significantly reduced from baseline to levels that were significantly lower than those in the historical controls but higher than those in uninfected patients. By contrast, protease inhibitors have been associated with a higher risk of cardiovascular disease and subclinical atherosclerosis [1–5], and these effects have been attributed at least in part to dyslipidemia [2]. The results of the SPIRAL study suggest that ritonavir-boosted protease inhibitor-containing therapy may be not only associated with increased plasma lipids but also with increased markers of inflammation, insulin resistance, and hypercoagulability relative to RAL-containing therapy. These findings are in accordance with previous studies showing associations between protease inhibitors and elevated fibrinogen levels in patients [9] and increased TNF-α and IL-6 expression in macrophages cultures [39]. Nevertheless, changes in biomarkers in SPIRAL study were marginally related to changes in lipids, therefore suggesting that protease inhibitor-related effects on cardiovascular biomarkers are not driven only by lipid changes.

In contrast to other biomarkers, we did not detect changes in markers of endothelial dysfunction. Although first-generation protease inhibitors were able to induce endothelial dysfunction through different pathways [11], contemporary protease inhibitors such as lopinavir/ritonavir or atazanavir have not been shown to induce endothelial dysfunction in healthy volunteers [40] or HIV-infected patients [41]. Because endothelial biomarkers are consistently elevated in HIV-infected compared with uninfected individuals despite effective antiretroviral therapy [42], the lack of changes in endothelial biomarkers in SPIRAL study participants switching from protease inhibitors to RAL may indicate that endothelial status reflected by endothelial markers was either unrelated to protease inhibitor therapy or unresponsive to protease inhibitor discontinuation.

The results of this substudy suggest differential effects in biomarkers between maintaining ritonavir-boosted protease inhibitors vs. switching them to RAL, but they should be interpreted with caution. In fact, therapy with nonnucleoside reverse transcriptase inhibitors such as efavirenz has been associated with higher levels of inflammation or immune activation markers than therapy with protease inhibitors in randomized trials of first-line therapies [19,43]. The clinical significance, if any, of these emerging data is unknown. This substudy had other limitations. Some markers had confirmed undetectable levels for a proportion of patients and this was particularly true for D-dimer; although an arbitrary value of the lower limit of detection was given for the purpose of computing changes, this was not an exact measurement. In addition, the percentage of change for D-dimer, although significant, was close to intra-assay variability, making its interpretation difficult. Finally, a number of different markers were studied, but there are other potentially important ones that were not assessed in this study.

In conclusion, switching from ritonavir-boosted protease inhibitors to RAL in the SPIRAL trial decreased biomarkers associated with inflammation and insulin resistance and these reductions were not completely explained by lipid changes. The results of this substudy should be viewed as hypothesis generating and need to be confirmed in future studies. Although this study and others suggest that there may be differential effects of antiretroviral therapies on cardiovascular biomarkers, the clinical relevance of these findings is currently unknown.

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Conflicts of interest

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Members of the SPIRAL Study Group: Trial chairs: José M. Gatell, María Larrousse, Esteban Martínez. Trial coordinators and monitors: Juan A. Arnaiz, Helena Beleta, David Garcia, Judit Pich, Andrea Pejenaute, Nuria Ramos. Trial statistician: Ignacio Pérez.

Participating centers and investigators (in alphabetical order): Hospital Universitario de Alicante, Alicante (V. Boix, L. Giner, J. Portilla). Hospital de Bellvitge, L'Hospitalet (D. Podzamczer, M. Saumoy). Hospital Clínic, Barcelona (J.L. Blanco, M. Calvo, J.M. Gatell, M. Laguno, M. Larrousse, M. Loncà, J. Mallolas, E. Martínez, M. Martínez-Rebollar, I. Pérez). Hospital Clínico de San Carlos, Madrid (V. Estrada). Hospital General Universitario de Elche, Elche (F. Gutiérrez, M. Masiá, S. Padilla, V. Sánchez). Hospital Germans Trías i Pujol, IrsiCaixa Foundation, Badalona (B. Clotet, R. Guerola, J.M. Llibre). Hospital General de Granollers, Granollers (E. Deig). Hospital Gregorio Marañón, Madrid (J. Berenguer, I. Gutiérrez, P. Miralles, M. Ramírez, M. Sanchez-Conde). Hospital Universitari de Tarragona Joan XXIII, Universitat Rovira i Virgili, Tarragona (J. Peraire, S. Veloso, F. Vidal, C. Viladés). Hospital del Mar, Barcelona (A. Gonzalez, H. Knobel, J. Villar). Hospital de Mataró, Mataró (P. Barrufet, L. Force). Hospital Parc Taulí, Sabadell (M.J. Amengual, E. Penelo, F. Segura). Hospital Universitario La Paz, Madrid (J.R. Arribas, J.M. Castro, M.L. Montes). Hospital Ramon y Cajal, Madrid (F. Dronda, S. Moreno). Hospital de Sant Pau, Barcelona (P. Domingo, M. Gutierrez, G. Mateo). Hospital Santiago, Santiago de Compostela (A. Antela, E. Losada, A. Prieto). Hospital Son Dureta, Palma de Mallorca (J. Murillas). Hospital Vall d'Hebron, Barcelona (A. Curran, E. Ribera).

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References

1. Holmberg SD, Moorman AC, Williamson JM, Tong TC, Ward DJ, Wood KC, *et al.* **Protease inhibitors and cardiovascular outcomes in patients with HIV-1.** *Lancet* 2002; **360**:1747–1748.
2. The DAD Study Group. **Class of antiretroviral drugs and the risk of myocardial infarction.** *N Engl J Med* 2007; **356**:1723–1735.
3. Lang S, Mary-Krause M, Cotte L, Gilquin J, Partisani M, Simno A, *et al.* **Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case–control study nested within the French Hospital Database on HIV ANRS cohort CO4.** *Arch Intern Med* 2010; **170**:1228–1238.
4. Currier JS, Lundgren JD, Carr A, Klein D, Sabin CA, Sax PE, *et al.* **Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy.** *Circulation* 2008; **118**:e29–e35.
5. Baker JV, Henry WK, Patel P, Bush TJ, Conley LJ, Mack WJ, Overton ET, *et al.* **Progression of carotid intima-media thickness in a contemporary human immunodeficiency virus cohort.** *Clin Infect Dis* 2011; **53**:826–835.
6. Hsu A, Granneman GR, Witt G, Locke C, Denissen J, Molla A, *et al.* **Multiple-dose pharmacokinetics of ritonavir in human immunodeficiency virus-infected subjects.** *Antimicrob Agents Chemother* 1997; **41**:898–905.
7. Shafran SD, Mashiter LD, Roberts SE. **The effect of low-dose ritonavir monotherapy on fasting serum lipid concentrations.** *HIV Med* 2005; **6**:421–425.
8. Reingold J, Wanke C, Lewis C, Tracy R, Heymsfield S, *et al.* **Association of HIV infection and HIV/HCV coinfection with C-reactive protein levels: the fat redistribution and metabolic change in HIV infection (FRAM) study.** *J Acquir Immune Defic Syndr* 2008; **48**:142–148.
9. Madden E, Lee G, Kotler DP, Wanke C, Lewis CE, Tracy RP, *et al.* **Association of antiretroviral therapy with fibrinogen levels in HIV-infection.** *AIDS* 2008; **22**:707–715.
10. Maggi P, Perilli F, Lillo A, Carito V, Epifani G, Bellacosa C, *et al.* **An ultrasound-based comparative study on carotid plaques in HIV-positive patients vs. atherosclerotic and arteritis patients: atherosclerotic or inflammatory lesions?** *Coron Artery Dis* 2007; **18**:23–29.
11. Wang X, Chai H, Yao Q, Chen C. **Molecular mechanisms of HIV protease inhibitor-induced endothelial dysfunction.** *J Acquir Immune Defic Syndr* 2007; **44**:493–499.
12. Hruz PW. **Molecular mechanisms for insulin resistance in treated HIV-infection.** *Best Pract Res Clin Endocrinol Metab* 2011; **25**:459–468.
13. Hui DY. **Effects of HIV protease inhibitor therapy on lipid metabolism.** *Prog Lipid Res* 2003; **42**:81–92.
14. Dressman J, Kincer J, Matveev SV, Guo L, Greenberg RN, *et al.* **HIV protease inhibitors promote atherosclerotic lesion formation independent of dyslipidemia by increasing CD36-dependent cholesteryl ester accumulation in macrophages.** *J Clin Invest* 2003; **111**:389–397.
15. Vasan SR. **Biomarkers of cardiovascular disease: molecular basis and practical considerations.** *Circulation* 2006; **113**:2335–2362.
16. Calmy A, Gayet-Ageron A, Montecucco F, Nguyen A, Mach F, Burger F, *et al.* **HIV increases markers of cardiovascular risk: results from a randomized, treatment interruption trial.** *AIDS* 2009; **23**:929–939.
17. Baker JV, Neuhaus J, Duprez D, Kuller LH, Tracy R, Belloso WH, *et al.* **Changes in inflammatory and coagulation biomarkers: a randomized comparison of immediate versus deferred antiretroviral therapy in patients with HIV infection.** *J Acquir Immune Defic Syndr* 2011; **56**:36–43.
18. Smith KY, Patel P, Fine D, Bellos N, Sloan L, Lackey P, *et al.* **Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavirfor initial HIV treatment.** *AIDS* 2009; **23**:1547–1556.
19. McComsey G, Kitch D, Daar E, Tierney C, Jahed N, Melbourne K, *et al.* **Inflammation markers after randomization to abacavir/lamivudine or tenofovir/emtricitabine with efavirenz or atazanavir/ritonavir.** *AIDS* 2012; **26**:1371–1385.
20. Delaugerre C, Ghosn J, Lacombe JM, Pialoux G, Cuzin L, Launay O, *et al.* **Trend over calendar time in virological failure in HIV-infected patients treated for at least six months with combined antiretroviral therapy in France (FHDH ANRS CO04).** In: *Proceedings of the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention*; 17–20 July 2011; Rome; abstract TUPDB0104.

21. Ross AC, Rizk N, O'Riordan MA, Dogra V, El-Bejjani D, Storer N, *et al.* **Relationship between inflammatory markers, endothelial activation markers, and carotid intima-media thickness in HIV-infected patients receiving antiretroviral therapy.** *Clin Infect Dis* 2009; **49**:1119–1127.
22. Sutherland JP, McKinley B, Eckel RH. **The metabolic syndrome and inflammation.** *Metab Syndr Relat Disord* 2004; **2**:82–104.
23. Martínez E, Larrousse M, Podzamczer D, Pérez I, Gutiérrez F, Loncá M, *et al.* **Abacavir-based therapy does not affect biological mechanisms associated with cardiovascular dysfunction.** *AIDS* 2010; **24**:F1–F9.
24. Martin A, Amin J, Cooper DA, Carr A, Kelleher AD, Bloch M, *et al.* **Abacavir does not affect circulating levels of inflammatory or coagulopathic biomarkers in suppressed HIV: a randomized clinical trial.** *AIDS* 2010; **24**:2657–2663.
25. Martínez E, Arnaiz JA, Podzamczer D, Dalmau D, Ribera E, Domingo P, *et al.* **Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection.** *N Engl J Med* 2003; **349**:1036–1046.
26. Eron JJ, Young B, Cooper DA, Youle M, Dejesus E, Andrade-Villanueva J, *et al.* **Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials.** *Lancet* 2010; **375**:396–407.
27. Martínez E, Larrousse M, Llibre JM, Gutiérrez F, Saumoy M, Antela A, *et al.* **Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study.** *AIDS* 2010; **24**:1697–1707.
28. Saumoy M, Ordoñez J, Martinez E, Llibre J, Ribera E, Knobel H, *et al.* **Comprehensive Lipid Evaluation in Patients Switching from PI/r-based cART to a RAL-based cART: The SPIRAL Substudy.** In: *Proceedings of the 18th Conference on Retroviruses and Opportunistic Infections (CROI)*; 27 February to 2 March 2011; Boston, Massachusetts; abstract 820.
29. Curran A, Martinez E, Saumoy M, Del Rio L, Crespo M, Larrousse M, *et al.* **Body composition changes after switching from protease inhibitors to raltegravir: SPIRAL-LIP substudy.** *AIDS* 2012; **26**:475–481.
30. Libby P. **Changing concepts of atherogenesis.** *J Intern Med* 2000; **247**:349–358.
31. Koenig W, Khuseyinova N. **Biomarkers of atherosclerotic plaque instability and rupture.** *Arterioscler Thromb Vasc Biol* 2007; **27**:15–26.
32. Neuhaus J, Jacobs DR, Baker JV, Calmy A, Duprez D, LaRosa A, *et al.* **Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection.** *J Infect Dis* 2010; **201**:1788–1795.
33. Rockstroh JK, Lennox JL, Dejesus E, Saag MS, Lazzarin A, Wan H, *et al.* **Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naive human immunodeficiency virus-1-infected patients: 156-week results from STARTMRK.** *Clin Infect Dis* 2011; **53**:807–816.
34. Samaras K, Ricardson R, Carr A. **Postprandial lipid effects of low-dose ritonavir vs. raltegravir in HIV-uninfected adults.** *AIDS* 2010; **24**:1727–1731.
35. Randell P, Jackson K, Dennis K, Moyle G. **The impact of raltegravir and lopinavir/ritonavir on peripheral glucose disposal in HIV-negative subjects.** *Antivir Ther* 2008; **13 (Suppl 4)**:A18.
36. Jackson K, Randell P, Milinkovic A, Boffito M, Moyle G. **A randomized comparison of raltegravir versus lopinavir/ritonavir on lipid subfractions and high-sensitivity C-reactive protein in healthy volunteers.** *Antivir Ther* 2012; **17 (Suppl 2)**:A17.
37. Silva E, Charreau I, Gourmel B, Mourah S, Kalidi I, Guillon B, *et al.* **Decrease in inflammatory and coagulation biomarkers in HIV+ patients after switching from enfuvirtide to raltegravir: the randomized ANRS 138 EASIER trial.** In: *Proceedings of the 19th Conference on Retroviruses and Opportunistic Infections (CROI)*; Seattle, Washington; 5–8 March 2012; abstract 840.
38. Pallikkuth S, Fischl M, Pahwa S. **Raltegravir therapy induces rapid decrease in immune activation, PD1 expression, and gut microbial translocation with increased recovery of central memory CD4 T cells in treatment-naïve patients with chronic HIV infection.** In: *Proceedings of the 19th Conference on Retroviruses and Opportunistic Infections (CROI)*; Seattle, Washington; 5–8 March 2012; abstract 277.
39. Zhou H, Jarujaron S, Gurley EC, Chen L, Ding H, Studer E, *et al.* **HIV protease inhibitors increase TNF-α and IL-6 expression in macrophages: involvement of the RNA-binding protein HuR.** *Atherosclerosis* 2007; **195**:e134–e143.
40. Dubé MP, Shen C, Greenwald M, Mather KJ. **No impairment of endothelial function or insulin sensitivity with 4 weeks of the HIV protease inhibitors atazanavir or lopinavir-ritonavir in healthy subjects without HIV infection: a placebo-controlled trial.** *Clin Infect Dis* 2008; **47**:567–574.
41. Solages A, Vita JA, Thornton DJ, Murray J, Heeren T, Craven DE, *et al.* **Endothelial function in HIV-infected persons.** *Clin Infect Dis* 2006; **42**:1325–1332.
42. Baker JV, Duprez D. **Biomarkers and HIV-associated cardiovascular disease.** *Curr Opin HIV AIDS* 2010; **5**:511–516.
43. Barqasho B, Abdurahman S, Nowak P, Vesterbacka J, Andersson LM, Svärd J, *et al.* **Longitudinal analysis of microbial translocation markers in patients on efavirenz and lopinavir/ritonavir-based ART.** In: *Proceedings of the 19th Conference on Retroviruses and Opportunistic Infections (CROI)*; Seattle, Washington; 5–8 March 2012; abstract 836.

ARTICLE 3

Abacavir/Lamivudine versus tenofovir/emtricitabine in virologically suppressed patients switching from ritonavir-boosted protease inhibitors to raltegravir.

Esteban Martínez, Polyana M. d'Albuquerque, Ignacio Pérez, Judit Pich and José M. Gatell.

Hospital Clínic-IDIBAPS, Universitat de Barcelona, Barcelona.

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Abacavir/Lamivudine Versus Tenofovir/Emtricitabine in Virologically Suppressed Patients Switching from Ritonavir-Boosted Protease Inhibitors to Raltegravir

Esteban Martínez, Polyana M. d'Albuquerque, Ignacio Pérez, Judit Pich, and José M. Gatell

Abstract

There are few clinical data on the combination abacavir/lamivudine plus raltegravir. We compared the outcomes of patients from the SPIRAL trial receiving either abacavir/lamivudine or tenofovir/emtricitabine at baseline who had taken at least one dose of either raltegravir or ritonavir-boosted protease inhibitors. For the purpose of this analysis, treatment failure was defined as virological failure (confirmed HIV-1 RNA ≥50 copies/ml) or discontinuation of abacavir/lamivudine or tenofovir/emtricitabine because of adverse events, consent withdrawal, or lost to follow-up. There were 143 (72.59%) patients with tenofovir/emtricitabine and 54 (27.41%) with abacavir/lamivudine. In the raltegravir group, there were three (11.11%) treatment failures with abacavir/lamivudine and eight (10.96%) with tenofovir/emtricitabine (estimated difference 0.15%; 95% CI −17.90 to 11.6). In the ritonavir-boosted protease inhibitor group, there were four (14.81%) treatment failures with abacavir/lamivudine and 12 (17.14%) with tenofovir/emtricitabine (estimated difference −2.33%; 95% CI −16.10 to 16.70). Triglycerides decreased and HDL cholesterol increased through the study more pronouncedly with abacavir/lamivudine than with tenofovir/emtricitabine and differences in the total-to-HDL cholesterol ratio between both combinations of nucleoside reverse transcriptase inhibitors (NRTIs) tended to be higher in the raltegravir group, although differences at 48 weeks were not significant. While no patient discontinued abacavir/lamivudine due to adverse events, four (2.80%) patients (all in the ritonavir-boosted protease inhibitor group) discontinued tenofovir/emtricitabine because of adverse events ($p=0.2744$). The results of this analysis do not suggest that outcomes of abacavir/lamivudine are worse than those of tenofovir/emtricitabine when combined with raltegravir in virologically suppressed HIV-infected adults.

Introduction

The efficacy of antiretroviral therapy has been improving over time allowing an increasing proportion of HIV-infected patients to achieve sustained suppression of viral replication in plasma. However, a considerable proportion of patients may still need to have their otherwise successful antiviral therapy changed because of comorbidities, drug–drug interactions, or other safety or convenience reasons.[1,2] Regimens preferentially recommended in major guidelines at present include a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third drug consisting of a nonnucleoside reverse transcriptase inhibitor (NNRTI), a ritonavir-boosted protease inhibitor (PI), or an integrase inhibitor.[3–6] These recommendations are based on major randomized clinical trials in antiretroviral-naive patients, but not all currently used drugs have been similarly tested in settings other than antiretroviral-naive patients or when tested have not shown the same level of evidence. Evidence-based guidance for the use of alternative drugs when considering changing a virologically successful antiretroviral regimen is often scarce.

Abacavir/lamivudine is a currently used fixed-dose combination of NRTIs, but data available with new drugs such as raltegravir are more limited than that of tenofovir/emtricitabine and in both cases are limited to antiretroviral-naive patients. Because abacavir/lamivudine and tenofovir/emtricitabine may have a different impact on comorbitities, choosing between them could be helpful to customize the optimal therapy. Ritonavir-boosted PIs are recommended agents for both antiretroviral-naive and antiretroviral-experienced patients because of their potency and high barrier to resistance,[3–6] but they may increase plasma lipids, have the potential for clinically meaningful drug–drug interactions,

Hospital Clínic-IDIBAPS, Universitat de Barcelona, Barcelona, Spain.

and have been associated with an increased risk for cardiovascular disease.[7–10] In HIV-infected adults with sustained virological suppression on ritonavir-boosted PIs, the SPIRAL study demonstrated that switching from ritonavir-boosted PIs to raltegravir did not result in less efficacy and did result in a better lipid profile at 48 weeks than continuing the ritonavir-boosted PI component.[11]

Although abacavir/lamivudine could be used like tenofovir/emtricitabine in combination with raltegravir in virologically suppressed HIV-infected patients, there are no data comparing the two combinations of NRTIs in this setting. To gather further insight on the abacavir/lamivudine plus raltegravir regimen in virologically suppressed treatment-experienced patients, we compared the efficacy and safety of abacavir/lamivudine to that of tenofovir/emtricitabine when each was combined with either raltegravir or ritonavir-boosted PIs in the SPIRAL trial.

Materials and Methods

The SPIRAL study was a 48-week, multicenter, open-label, randomized trial in which HIV-infected adults with <50 copies/ml of plasma HIV RNA for at least the previous 6 months on ritonavir-boosted PI-based therapy were randomized (1:1) to switch from the ritonavir-boosted PI to raltegravir or to continue on ritonavir-boosted PI-based therapy. The protocol was approved by the Ethics Committee at each center and by the Spanish Medicines Evaluation Agency. Written informed consent was obtained from all eligible patients before randomization. The SPIRAL trial is registered with ClinicalTrials.gov number NCT00528892. This analysis was planned after the parent study had been finished because abacavir/lamivudine and tenofovir/emtricitabine were the combinations of NRTIs most commonly used in the SPIRAL study and because of the paucity of data on the combination of abacavir/lamivudine plus raltegravir. For the purpose of this analysis, eligible patients were those who were receiving either abacavir/lamivudine or tenofovir/emtricitabine at baseline and who received at least one dose of either raltegravir or ritonavir-boosted PI. Patients were already taking the combinations of abacavir/lamivudine or tenofovir/emtricitabine when they were included in the SPIRAL study, and for this reason all of them were able to tolerate them. As the analysis did not ensure the homogeneity of the baseline characteristics between groups, comparisons in outcomes between groups were adjusted for differences in baseline characteristics.

Treatment failure was considered in all patients who had virological failure or discontinued abacavir/lamivudine or tenofovir/emtricitabine because of adverse events, consent withdrawal, or lost to follow-up. Virological failure was defined by a confirmed plasma HIV-1 RNA ≥50 copies/ml during treatment, whereas patients who withdrew consent, were lost, or switched or stopped abacavir/lamivudine or tenofovir/emtricitabine were censored. A sensitivity analysis for efficacy endpoints was done including all randomized patients. Fisher's exact test was used to compare proportions between treatment groups. The Mann–Whitney *U*-test was used for comparisons of continuous variables between groups. For testing overall differences of abacavir/lamivudine relative to tenofovir/emtricitabine and stratified by raltegravir and ritonavir-boosted PI use, 95% confidence intervals for the treatment difference were calculated by Newcombe's method.[12] Simple comparisons were made with use of a two-sided alpha level of 0.05. Statistical analyses were performed with the use of SAS version 9.1.3 (SAS Institute, Cary, NC). The sponsors of the SPIRAL trial had no role in the study design, data collection, analysis, interpretation, or writing of this report. Esteban Martínez, Judit Pich, and Ignacio Perez had full access to all the data and had the final responsibility for the decision to submit this report for publication.

Results

Baseline characteristics

Of the 273 patients included in the SPIRAL study, 197 (72.16%) were included in this analysis. There were 143 (72.59%) patients treated with tenofovir/emtricitabine and 54 (27.41%) with abacavir/lamivudine. Tenofovir/emtricitabine and abacavir/lamivudine accounted for 76.56% of the combinations of NRTIs used in the SPIRAL study. In the overall population, patients taking abacavir/lamivudine were older, had a lower prevalence of previous virological failure, and had higher plasma levels of triglycerides, total and HDL cholesterol than patients taking tenofovir/emtricitabine (Table 1A). Baseline characteristics in the raltegravir and ritonavir-boosted PI groups are shown in Table 1B. In the population assigned to raltegravir (Table 1B), patients taking abacavir/lamivudine were significantly older and a higher proportion had suffered previous virological failure than those taking tenofovir/emtricitabine.

Efficacy

There were no deaths or new AIDS-defining events. In the overall population, there were 7/54 (12.96%) treatment failures in the abacavir/lamivudine group (three virological failures and four abacavir/lamivudine discontinuations) and 20/143 (14%) in the tenofovir/emtricitabine group (seven virological failures and 13 tenofovir/emtricitabine discontinuations) (estimated difference −1.02%; 95% confidence interval −10.30 to 11.40). In the raltegravir group, there were 3/27 (11.11%) treatment failures in the abacavir/lamivudine group and 8/73 (10.96%) in the tenofovir/emtricitabine group (estimated difference 0.15%; 95% confidence interval −17.90 to 11.6). In the ritonavir-boosted PI group, there were 4/27 (14.81%) treatment failures in the abacavir/lamivudine group and 12/70 (17.14%) in the tenofovir/emtricitabine group (estimated difference −2.33%; 95% confidence interval −16.10 to 16.70). Additional efficacy analyses according to prior virological failure or suboptimal therapy and a sensitivity analysis including all randomized patients did not significantly affect the overall results (data not shown).

In the overall population, there were 3/54 (5.56%) virological failures in the abacavir/lamivudine group and 7/143 (4.90%) in the tenofovir/emtricitabine group (estimated difference 0.66%; 95% confidence interval −10.50 to 5.40). In the raltegravir group, there were 1/27 (3.70%) virological failures in the abacavir/lamivudine group and 3/73 (4.11%) in the tenofovir/emtricitabine group (estimated difference −0.41%; 95% confidence interval −8.30 to 14.4). In the ritonavir-boosted PI group, there were 2/27 (7.41%) virological failures in the abacavir/lamivudine group and 4/70 (5.71%) in the

TABLE 1A. DEMOGRAPHIC AND BASELINE CHARACTERISTICS (ABACAVIR/LAMIVUDINE VS. TENOFOVIR/EMTRICITABINE)

	Abacavir/lamivudine (n = 54)		*Tenofovir/emtricitabine* (n = 143)		p-*value*
Age, years [median (IQR)]	46.5	(42–56)	44	(40–48)	0.0054
Female sex [*n* (%)]	10	(18.52)	27	(25.87)	0.48
Ritonavir-boosted protease inhibitors at entry [*n* (%)]					
Lopinavir/ritonavir	25	(46.3)	68	(47.55)	
Atazanavir/ritonavir	20	(37.04)	47	(32.87)	
Fosamprenavir/ritonavir	9	(16.67)	14	(9.79)	
Saquinavir/ritonavir	—	(0)	2	(1.4)	
Darunavir/ritonavir	—	(0)	1	(0.7)	
Tipranavir/ritonavir	—	(0)	1	(0.7)	
Patients on their first antiretroviral regimen [*n* (%)]	9	(16.67)	18	(12.59)	0.48
Exposure to antiretroviral therapy (years) [median (range)]	9.17	(4–11.77)	10.13	(3.7–12.76)	0.56
Exposure to protease inhibitor-based therapy (months) [median (range)]	28	(15.52–44.03)	29.22	(18.53–36.23)	0.92
Patients with previous suboptimal antiretroviral therapy [*n* (%)]	15	(27.78)	55	(38.46)	0.18
Patients with previous virological failure [*n* (%)]	7	(12.96)	54	(37.76)	<0.001
Patients with previous suboptimal antiretroviral therapy or virological failure [*n* (%)]	19	(35.19)	70	(48.95)	0.10
Number of previous antiretroviral regimens [median (IQR)]	4	(2–7)	5	(2–7.5)	0.71
Number of previous suboptimal antiretroviral regimens [median (IQR)]	2	(1–2)	2	(1–3)	0.41
Number of previous virological failures [median (IQR)]	2	(1–2)	1	(1–3)	0.86
Patients with AIDS [*n* (%)]	25	(0.7)	71	50	0.75
CD4 cell count (cells/ml) [median (IQR)]	514.5	(375.15–779.7)	486.5	(355.5–720)	0.52
CD8 cell count (cells/ml) [median (IQR)]	761.91	(577.98–1085.76)	799	(575–1071.33)	0.946
Triglycerides (mg/dl) [median (IQR)]	193	(150.58–268)	153.5	(103–238)	0.007
Triglycerides >200 mg/dl [*n* (%)]	23	(42.59)	48	(33.57)	0.24
Total cholesterol (mg/dl) [median (IQR)]	219.3	(193–242)	193.5	(167.5–221)	0.001
Total cholesterol >240 mg/dl [*n* (%)]	14	(25.93)	17	(11.89)	0.026
LDL cholesterol (mg/dl) [median (IQR)]	129.5	(107.25–149.25)	119	(96–146)	0.20
LDL cholesterol >160 mg/dl [*n* (%)]	16.67	(54)	11.19	(143)	0.33
HDL cholesterol (mg/dl) [median (IQR)]	49.62	(38.85–57.31)	42.31	(34–52.7)	0.008
HDL cholesterol <40 mg/dl [*n* (%)]	15	(27.78)	55	(38.46)	0.18
Lipid-lowering therapy at entry [*n* (%)]	14	(25.93)	19	(13.29)	0.052

tenofovir/emtricitabine group (estimated difference 1.69%; 95% confidence interval −18.00 to 8.00). Again, additional efficacy analyses according to prior virological failure or suboptimal therapy and a sensitivity analysis including all randomized patients did not significantly affect the overall results (data not shown).

At 48 weeks, CD4 cells (mean ± SD) increased 55.74 (± 227.70) per mm^3 in the abacavir/lamivudine group and 50.14 (± 162.47) per mm^3 in the tenofovir/emtricitabine group ($p = 0.5992$). In the raltegravir group, CD4 cells (mean ± SD) increased 33.34 (187.86) per mm^3 in the abacavir/lamivudine group and 27.89 (± 170.14) per mm^3 in the tenofovir/emtricitabine group ($p = 0.6794$) at 48 weeks. In the ritonavir-boosted PI group, CD4 cells (mean ± SD) increased 79.92 (± 266.02) per mm^3 in the abacavir/lamivudine group and 74.48 (± 151.23) per mm^3 in the tenofovir/emtricitabine group ($p = 0.7329$) at 48 weeks.

Safety

At 48 weeks, changes in triglycerides (mean percent change, −17.65% vs. −18.12%, $p = 0.4224$), total cholesterol (mean percent change, −7.38% vs. −5.00%, $p = 0.4874$), LDL cholesterol (mean percent change, −12.22% vs. −5.33%, $p = 0.5291$), HDL cholesterol (mean percent change, +0.72% vs. −2.56%, $p = 5661$), and total-to-HDL cholesterol ratio (mean percent change, −0.49 vs. −0.17, $p = 0.1747$) were not significantly different between the abacavir/lamivudine and tenofovir/emtricitabine groups, respectively. At 48 weeks, the proportion of patients showing triglycerides >200 mg/dl ($n = 12$, 22.64% vs. $n = 29$, 21.01%, $p = 0.8449$), total cholesterol >240 mg/dl ($n = 8$, 15.09% vs. $n = 8$, 5.80%, $p = 0.0753$), or LDL cholesterol >160 mg/dl ($n = 1$, 1.89% vs. $n = 4$, 2.90%, $p = 1$) was not different between the abacavir/lamivudine or tenofovir/emtricitabine groups, respectively.

However, the proportion of patients showing HDL cholesterol <40 mg/dl at 48 weeks was significantly lower with abacavir/lamivudine ($n = 11$, 20.75%) relative to that with tenofovir/emtricitabine ($n = 63$, 45.65%) ($p = 0.0016$). Median changes in plasma lipids in patients receiving either abacavir/lamivudine or tenofovir/emtricitabine in combination with raltegravir or ritonavir-boosted PI are shown in Fig. 1. As expected, decreases in plasma lipids were higher in patients switching from ritonavir-boosted PIs to raltegravir than in those continuing on ritonavir-boosted PIs. Interestingly, decreases in triglycerides and increases in HDL cholesterol through the study tended to be more pronounced in patients receiving abacavir/lamivudine than in those receiving tenofovir/emtricitabine, and differences in the total-to-HDL

TABLE 1B. DEMOGRAPHIC AND BASELINE CHARACTERISTICS (ABACAVIR/LAMIVUDINE VS. TENOFOVIR/EMTRICITABINE IN RALTEGRAVIR AND RITONAVIR-BOOSTED PROTEASE INHIBITOR GROUPS)

	Raltegravir					*Ritonavir-boosted protease inhibitor*				
	Abacavir/ lamivudine (n=27)		*Tenofovir/ emtricitabine (n=73)*		*p-value*	*Abacavir/ lamivudine (n=27)*		*Tenofovir/ emtricitabine (n=70)*		*p-value*
Age, years [median (IQR)]	47	(43–60)	44	(39–48)	0.002	45	(38–52)	44	(40–48)	0.68
Female sex [*n* (%)]	3	(11.11)	17	(23.29)	0.26	7	(25.93)	20	(28.57)	1
Ritonavir-boosted protease inhibitors at entry [*n* (%)]										
Lopinavir/ritonavir	11	(40.74)	35	(47.95)		14	(51.85)	33	(47.14)	
Atazanavir/ritonavir	11	(40.74)	25	(34.25)		9	(33.33)	22	(31.43)	
Fosamprenavir/ritonavir	5	(18.52)	7	(9.59)		4	(14.81)	7	(10)	
Saquinavir/ritonavir	—	(0)	3	(4.11)		—	(0)	8	(11.43)	
Darunavir/ritonavir	—	(0)	1	(1.37)						
Tipranavir/ritonavir	—	(0)	1	(1.37)						
Patients on their first antiretroviral regimen [*n* (%)]	4	(14.81)	10	(13.7)	1	5	(18.52)	8	(11.43)	0.50
Exposure to antiretroviral therapy (years) [median (range)]	10.65	(5.02–12.73)	9.22	(2.7–12.33)	0.39	8.17	(3.81–10.89)	10.73	(4.44–13.15)	0.05
Exposure to protease inhibitor-based therapy (months) [median (range)]	29.4	(19.53–45.23)	29.55	(18.23–35.67)	0.58	27.78	(13–39.73)	29.02	(19–37.93)	0.48
Patients with previous suboptimal antiretroviral therapy [*n* (%)]	11	(40.74)	26	(35.62)	0.64	4	(14.81)	29	(41.43)	0.01
Patients with previous virological failure [*n* (%)]	4	(14.81)	28	(38.36)	0.033	3	(11.11)	26	(37.14)	0.01
Patients with previous suboptimal antiretroviral therapy or virological failure [*n* (%)]	14	(51.85)	35	(47.95)	0.82	5	(18.52)	35	(50)	<0.001
Number of previous antiretroviral regimens [median (IQR)]	5.5	(2–9)	4	(2–6)	0.22	4	(2–4)	5	(3–8)	0.04
Number of previous suboptimal antiretroviral regimens [median (IQR)]	2	(1–3)	2	(1–3)	0.76	1.5	(1–2)	2	(1–3)	0.31
Number of previous virological failures [median (IQR)]	1.5	(1–2)	1	(1–3)	0.73	2	(1–4)	1	(1–2)	0.48
Patients with AIDS [*n* (%)]	11	(40.74)	37	(50.68)	0.05	14	(51.84)	34	(48.57)	0.82
CD4 cell count (cells/ml) [median (IQR)]	565.5	(416–806)	477.4	(348.14–731.4)	0.23	467.04	(350.4–735.05)	501	(384–685.1)	0.76
CD8 cell count (cells/ml) [median (IQR)]	845.34	(577.98–1275)	832.8	(680.95–1071.9)	0.78	756	(577.5–974.4)	718.1	(504–1071.33)	0.558781
Triglycerides (mg/dl) [median (IQR)]	168.29	(149.9–268)	151.29	(100.5–242.5)	0.11	198	(150.58–282)	157	(104–231.15)	0.02
Triglycerides >200 mg/dl [*n* (%)]	10	(37.04)	25	(34.25)	0.81	13	(48.15)	23	(32.86)	0.17
Total cholesterol (mg/dl) [median (IQR)]	217.69	(193–244)	198	(168.5–226.5)	0.04	221	(187–242)	190.5	(167.5–217.5)	<0.001
Total cholesterol >240 mg/dl [*n* (%)]	7	(25.93)	9	(12.33)	0.12	7	(25.93)	8	(11.43)	0.11
LDL cholesterol (mg/dl) [median (IQR)]	128.5	(108.5–139)	124	(95.8–147)	0.83	138.46	(100–163)	113	(96.9–144)	0.12
LDL cholesterol >160 mg/dl [*n* (%)]	9	(33.33)	28	(38.36)	0.81	6	(22.22)	27	(38.57)	0.15
HDL cholesterol (mg/dl) [median (IQR)]	45	(38.85–58.85)	44.7	(33–54)	0.19	49.81	(41–56)	41.62	(34.25–49.35)	0.01
HDL cholesterol <40 mg/dl [*n* (%)]	2	(7.41)	12	(16.44)	0.34	7	(25.93)	4	(5.71)	<0.001
Lipid-lowering therapy at entry [*n* (%)]	5	(18.52)	8	(10.96)	0.32	9	(33.33)	11	(15.71)	0.09

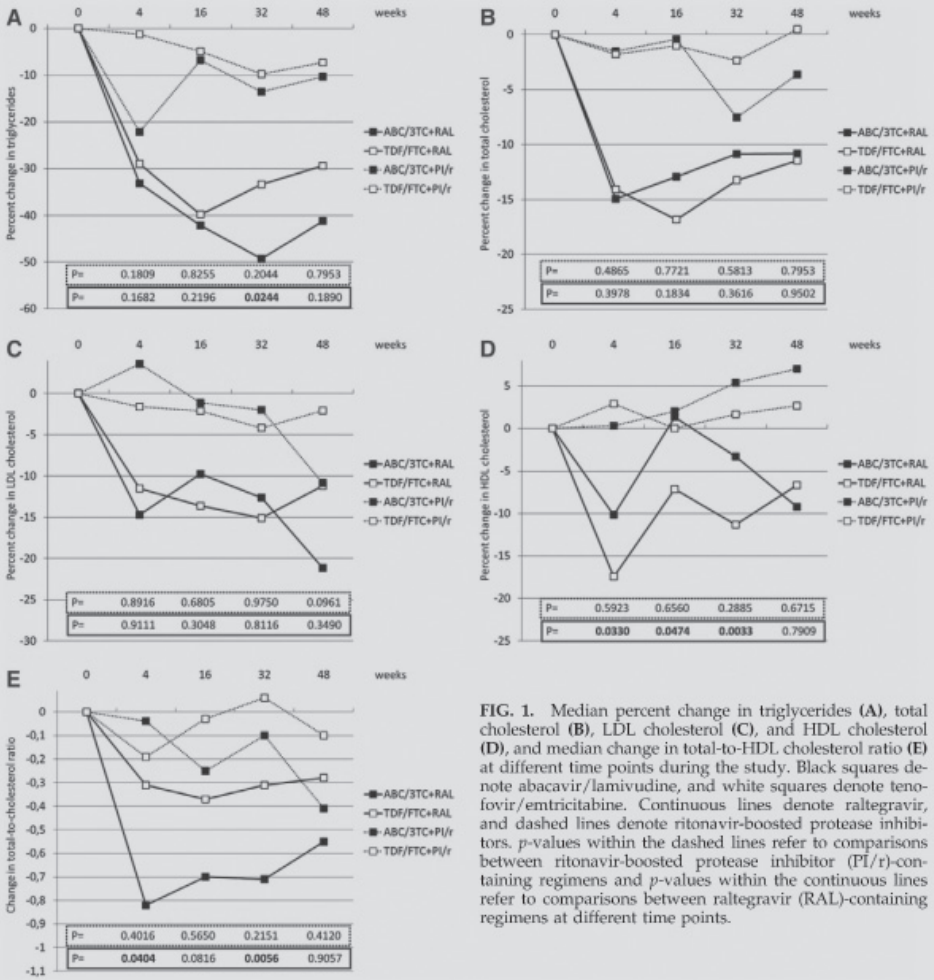

FIG. 1. Median percent change in triglycerides **(A)**, total cholesterol **(B)**, LDL cholesterol **(C)**, and HDL cholesterol **(D)**, and median change in total-to-HDL cholesterol ratio **(E)** at different time points during the study. Black squares denote abacavir/lamivudine, and white squares denote tenofovir/emtricitabine. Continuous lines denote raltegravir, and dashed lines denote ritonavir-boosted protease inhibitors. *p*-values within the dashed lines refer to comparisons between ritonavir-boosted protease inhibitor (PI/r)-containing regimens and *p*-values within the continuous lines refer to comparisons between raltegravir (RAL)-containing regimens at different time points.

cholesterol ratio between both combinations of NRTIs tended to be higher in the raltegravir group, although differences at 48 weeks were not significant in any case (Fig. 1). Four (7.41%) patients treated with abacavir/lamivudine and seven (4.90%) patients treated with tenofovir/emtricitabine discontinued lipid-lowering therapies during the study ($p=0.4972$).

The overall incidence of adverse effects was similar in the abacavir/lamivudine ($n=33$, 61.11%) and the tenofovir/emtricitabine ($n=82$, 57.34%) groups ($p=0.6335$). Although no patient discontinued abacavir/lamivudine due to adverse events, four (2.80%) patients (all in the ritonavir-boosted PI group) discontinued tenofovir/emtricitabine because of kidney (progressive decrease in glomerular filtration rate, $n=3$) or bone (progressive decrease in bone mineral density, $n=1$) events ($p=0.2744$).

Discussion

This analysis of the SPIRAL trial suggests that abacavir/lamivudine may display similar efficacy and be as well tolerated as tenofovir/emtricitabine when combined with raltegravir in virologically suppressed HIV-infected adults. Prior comparisons between both fixed-dose NRTI combinations in virologically suppressed HIV-infected adults have also shown similar results in the BICOMBO and STEAL trials,[13,14] although in the BICOMBO trial there were more

discontinuations with abacavir/lamivudine due to hypersensitivity because patients had not been previously tested for HLA-B5701. In the SPIRAL study, patients taking abacavir/lamivudine or tenofovir/emtricitabine had been taking these combinations for months or years and therefore they were already able to tolerate them.

Approximately 40% of treatment failures in the abacavir/lamivudine and tenofovir/emtricitabine groups in the SPIRAL trial were due to virological failure. There are no available data on the use of raltegravir combined with tenofovir/emtricitabine or abacavir/lamivudine in other than antiretroviral-naive patients. In combination with tenofovir/emtricitabine, raltegravir ($n=281$) demonstrated no inferiority when compared with efavirenz ($n=282$) in the STARTMRK study (53% of the patients had HIV-1 RNA >100,000 copies/ml). The proportion of patients treated with tenofovir/emtricitabine plus raltegravir showing HIV-1 RNA <50 copies/ml was 86% at 48 weeks, 81% at 96 weeks, and 75% at 156 weeks.[15–17] Data with abacavir/lamivudine plus raltegravir are more limited. The SHIELD trial (34% of the patients had HIV-1 RNA >100,000 copies/ml) was a prospective, observational study enrolling 35 antiretroviral-naive patients who initiated abacavir/lamivudine plus raltegravir. The proportion of patients showing HIV-1 RNA <50 copies/ml was 91% at 48 weeks and 77% at 96 weeks.[18,19]

In accordance with other studies comparing abacavir/lamivudine and tenofovir/emtricitabine, patients taking abacavir/lamivudine showed higher plasma lipids at baseline as compared to patients taking tenofovir/emtricitabine.[13,14,20–22] Although differences were not significant at 48 weeks, it may be of interest that through the study decreases in triglycerides, decreases in total-to-HDL cholesterol, and increases in HDL cholesterol tended to be higher when raltegravir (instead of ritonavir-boosted PIs) was combined with abacavir/lamivudine than with tenofovir/emtricitabine. This was also consistent with a significantly lower proportion of patients showing HDL cholesterol <40 mg/dl at 48 weeks when treated with abacavir/lamivudine compared to tenofovir/emtricitabine, and a nonsignificant higher decrease in the total-to-HDL cholesterol ratio at 48 weeks in patients treated with abacavir/lamivudine plus raltegravir relative to patients treated with tenofovir/emtricitabine plus raltegravir.

These data suggest that the improvement in plasma lipids expected when PIs are replaced by raltegravir in virologically suppressed HIV-infected patients should not be worse when the combination of NRTIs used is abacavir/lamivudine than when it is tenofovir/lamivudine. This finding was unexpected and the reason is not clear. Potential explanations might be that baseline lipids with abacavir/lamivudine were already higher that those with tenofovir/emtricitabine when combined with ritonavir-boosted protease inhibitors and/or that the lipid-lowering effect of discontinuing ritonavir-boosted protease inhibitors may be greater with abacavir/lamivudine than with tenofovir/emtricitabine. However, these results should be taken with caution because of the small sample size and the lack of significance at 48 weeks in most lipid changes. Nevertheless, because of the paucity of data concerning the combination of abacavir/lamivudine plus raltegravir and because the design of the SPIRAL study included only antiretroviral-experienced, virologically suppressed HIV-infected patients, it would make sense to accurately investigate the lipid profile in future studies assessing the effects of this antiretroviral combination in other patient settings.

There were no discontinuations of any combination of NRTIs due to adverse events when combined with raltegravir. In patients taking ritonavir-boosted PIs, four patients discontinued tenofovir/emtricitabine due to adverse events as compared to no patient discontinuing abacavir/lamivudine. Although this difference was not significant, the results are not unexpected due to the negative impact of protease inhibitors on tenofovir-related kidney or bone toxicity.[23,24]

The small sample size of the abacavir-lamivudine group is a limitation of the study. However, the only existing data on the combination abacavir/lamivudine plus raltegravir included 35 antiretroviral-naive patients, and thus the number of patients with this combination of interest was almost double in our study. The NRTI backbone was not the randomized component, although comparisons in outcomes were adjusted for baseline characteristics showing differences between groups. In addition, the analyses of efficacy outcomes may have been affected by the reduced power given to the relatively low frequency of the outcome measures. However, the study has also strengths as there are few data on the combination abacavir/lamivudine plus raltegravir and the data available are restricted to antiretroviral-naive patients.

In summary, this analysis of the SPIRAL trial does not suggest that outcomes of abacavir/lamivudine are worse than those of tenofovir/emtricitabine when combined with raltegravir in virologically suppressed HIV-infected adults.

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E. Martínez and J.M. Gatell designed the study, helped with analyses of data, and drafted the manuscript. P.M. d'Albuquerque and J. Pich helped design the study, interpreted results, and drafted and revised the manuscript. I. Pérez performed statistical analyses and led the interpretation of the results. All authors critically reviewed and subsequently approved the final version.

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References

1. Vo TT, Ledergerber B, Keiser O, Hirschel B, Furrer H, Battegay M, *et al.*: Durability and outcome of initial

antiretroviral treatments received during 2000–2005 by patients in the Swiss HIV Cohort Study. J Infect Dis 2008;197:1685–1694.
2. Gazzola L, Tincati C, and d'Arminio Monforte A: Non-infectious HIV-related comorbidities and HAART toxicities: Choosing alternative antiretroviral strategies. HIV Ther 2010; 5:553–565.
3. Thompson MA, Aberg JA, Cahn P, Montaner JS, Rizzardini G, Telenti A, *et al.*: Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel. JAMA 2010;304:321–333.
4. Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. October 14, 2011. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed May 25, 2012.
5. European AIDS Clinical Society Guidelines: Version 6–October 2011. Available at http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/eacsguidelines-v6_english.pdf. Accessed May 25, 2012.
6. Panel de expertos de GESIDA y Plan Nacional sobre el Sida: National consensus document by GESIDA/National AIDS Plan on antiretroviral treatment in adults infected by the human immunodeficiency virus (January 2011 update). Enferm Infecc Microbiol Clin 2011;29:209.e1-103.
7. Moyle GJ and Back D: Principles and practice of HIV-protease inhibitor pharmacoenhancement. HIV Med 2001;2: 105–113.
8. The DAD Study Group: Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007;356: 1723–1735.
9. Hsu A, Granneman GR, Witt G, Locke C, Denissen J, Molla A, *et al.*: Multiple-dose pharmacokinetics of ritonavir in human immunodeficiency virus-infected subjects. Antimicrob Agents Chemother 1997;41:898–905.
10. Shafran SD, Mashiter LD, and Roberts SE: The effect of low-dose ritonavir monotherapy on fasting serum lipid concentrations. HIV Med 2005;6:421–425.
11. Martinez E, Larrousse M, Llibre JM, Gutierrez F, Saumoy M, Antela A, *et al.*: Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: The SPIRAL study. AIDS 2010;24:1697–1707.
12. Newcombe RG: Interval estimation for the difference between independent proportions: Comparison of eleven methods. StatMed 1998;17:873–890.
13. Martinez E, Arranz JA, Podzamczer D, Loncá M, Sanz J, Barragán P, *et al.*: A simplification trial switching from nucleoside reverse transcriptase inhibitors to once-daily fixed-dose abacavir/lamivudine or tenofovir/emtricitabine in HIV-1-infected patients with virological suppression. J Acquir Immune Defic Syndr 2009;51:290–297.
14. Martin A, Bloch M, Amin J, Baker D, Cooper DA, Emery S, *et al.*: Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: A randomized, 96-week trial. Clin Infect Dis 2009;49:1591–1601.
15. Lennox JL, DeJesus E, Lazzarin A, Pollard RB, Madruga JV, Berger DS, *et al.*: Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: A multicentre, double-blind randomised controlled trial. Lancet 2009;374:796–806.
16. Lennox JL, Dejesus E, Berger DS, Lazzarin A, Pollard RB, Ramalho Madruga JV, *et al.*: Raltegravir versus efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. J Acquir Immune Defic Syndr 2010;55:39–48.
17. Rockstroh JK, Lennox JL, Dejesus E, Saag MS, Lazzarin A, Wan H, *et al.*: Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naive human immunodeficiency virus-1-infected patients: 156-week results from STARTMRK. Clin Infect Dis 2011;53:807–816.
18. Young B, Vanig T, Dejesus E, Hawkins T, St Clair M, Yau L, *et al.*: A pilot study of abacavir/lamivudine and raltegravir in antiretroviral-naïve HIV-1-infected patients: 48-week results of the SHIELD trial. HIV Clin Trials 2010;11:260–269.
19. Young B, Vanig T, Dejesus E, Hawkins T, St Clair M, Stancil B, *et al.*: 96-week results of a pilot study of abacavir/lamivudine and raltegravir in antiretroviral-naïve HIV-1-infected patients: The SHIELD trial. HIV Clin Trials 2010;12:228–233.
20. Smith KY, Patel P, Fine D, Bellos N, Sloan L, Lackey P, *et al.*: Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. AIDS 2009; 23:1547–1556.
21. Sax PE, Tierney C, Collier AC, Fischl MA, Mollan K, Peeples L, *et al.*: Abacavir-lamivudine versus tenofovir-emtricitabine for initial HIV-1 therapy. N Engl J Med 2009;361:2230–2240.
22. Post FA, Moyle GJ, Stellbrink HJ, Domingo P, Podzamczer D, Fisher M, *et al.*: Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. J Acquir Immune Defic Syndr 2010;55:49–57.
23. Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, *et al.*: Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS 2010;24:1667–1678.
24. Bedimo R, Maalouf NM, Zhang S, Drechsler H, and Tebas P: Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS 2012;26:825–831.

Address correspondence to:
Esteban Martínez
Infectious Diseases Unit
Hospital Clínic
University of Barcelona
08036 Barcelona
Spain

E-mail: esteban@fundsoriano.es

ARTICLE 4

Rosuvastatin versus protease inhibitor switching for hypercholesterolaemia: a randomised trial.

Frederick J. Lee [1], Polyana Monteiro [2], David Baker [3], Mark Bloch [4], Norman Roth [5], Robert Finlayson [6], Richard Moore [7], Jennifer Hoy [8], Esteban Martinez [2], Andrew Carr [1] .

[1] Clinical Research Program, Centre for Applied Medical Research, St Vincent's Hospital, Sydney, Australia; [2] Infectious Diseases Unit, Hospital Cliníc, University of Barcelona, Barcelona, Spain; [3] East Sydney Doctors, Sydney, Australia; [4] Holdsworth House Medical Practice, Sydney, Australia; [5] Prahran Market Clinic, Melbourne, Australia; [6] Taylor Square Private Clinic, Sydney, Australia; [7] Northside Clinic, Melbourne, Australia; [8] Department of Infectious Diseases, The Alfred Hospital & Monash University, Melbourne, Australia.

Submitted.

Rosuvastatin versus protease inhibitor switching for hypercholesterolaemia: a randomised trial

(Short title: Statin vs. PI/r switch for hypercholesterolaemia)

Frederick J. Lee[1], Polyana Monteiro[2], David Baker[3], Mark Bloch[4], Norman Roth[5], Robert Finlayson[6], Richard Moore[7], Jennifer Hoy[8], Esteban Martinez[2], Andrew Carr[1]

[1] Clinical Research Program, Centre for Applied Medical Research, St Vincent's Hospital, Sydney, Australia [2] Infectious Diseases Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain [3] East Sydney Doctors, Sydney, Australia [4] Holdsworth House Medical Practice, Sydney, Australia [5] Prahran Market Clinic, Melbourne, Australia [6] Taylor Square Private Clinic, Sydney, Australia [7] Northside Clinic, Melbourne, Australia [8] Department of Infectious Diseases, The Alfred Hospital & Monash University, Melbourne, Australia

Abstract

Background Optimal management of hypercholesterolaemia in adults on ritonavir-boosted protease inhibitors (PI/rs) is unknown. The proven options – statins and PI/r switching – have not been compared for current drugs.

Methods HIV-1-infected adults on PI/r-based therapy with viral load <50 copies/mL, fasting total cholesterol ≥5.5 mmol/L, elevated cardiovascular risk (Framingham score ≥8% or diabetes or family history of premature cardiovascular disease), and not on lipid-lowering therapy were randomised to open-label rosuvastatin 10 mg/day or to PI/r switching, both with standardised diet/exercise advice. The primary endpoint was change in total cholesterol at week 12 (intention-to-treat).

Findings 43 participants (23 rosuvastatin); baseline characteristics (mean [SD] or n [%]): age 55 (8.5) years; 42 (98%) male; 41 (95%) white race; and total cholesterol 6.2 (1.2) mmol/L. At enrolment, PI/rs were lopinavir/ritonavir (n=22; 51%), atazanavir/ritonavir (n=12; 28%) and darunavir/ritonavir (n=9; 21%). Commonest PI/r substitutes were raltegravir (n=9; 45%) and rilpivirine (n=4, 20%). All participants were adherent through to week 12. Rosuvastatin yielded greater declines in total (-21.4% vs. -8.7%, p=0.003) and low-density lipoprotein (-29.9% vs. -1.0%, p<0.001) cholesterol, but lesser declines in very low-density lipoprotein cholesterol and triglycerides (p<0.01). Cholesterol-lowering was greater in participants on atazanavir/ritonavir or once-daily darunavir/ritonavir (vs. lopinavir/ritonavir) . More study drug-related adverse events (mostly grade 1 nausea/diarrhoea; 10 vs. 1, p=0.001) occurred with PI/r switching.

Interpretation In adults receiving a PI/r, rosuvastatin 10 mg/day for 12 weeks yielded larger decreases in total and LDL cholesterol than PI/r switching, and was better tolerated.

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Keywords cardiovascular risk; HIV; hypercholesterolaemia; protease inhibitors; statins; switch study

Introduction

Dyslipidaemia is a well-documented complication of ritonavir-boosted protease inhibitor (PI/r) therapy, leading to increases in fasting total, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) cholesterol fractions and in triglycerides, but with minimal effect upon high-density lipoprotein (HDL) cholesterol concentrations.[1, 2] Earlier PI/rs (particularly indinavir and lopinavir/ritonavir) have been independently associated with a 12% to 16% increased relative risk of myocardial infarction per year of exposure.[3, 4]

The current preferred PI/r options are atazanavir/ritonavir and once-daily darunavir/ritonavir.[5] To date, atazanavir has not been associated with greater incidence of cardiovascular events,[6] while no similar analysis is available for darunavir/ritonavir. Yet both

of these PI/rs produce elevations in total and LDL cholesterol and triglycerides relative to the integrase strand transfer inhibitor raltegravir.[7]

PI/r-associated hypercholesterolaemia may be managed either by: (1) lipid-lowering therapy; or (2) replacing the PI/r with an alternative antiretroviral drug with fewer dyslipidaemic effects (PI/r switching). Amongst lipid-lowering drugs, statins have an established role for reducing total and LDL cholesterol, and preventing cardiovascular events in the general population.[8, 9] Adding a statin increases pill burden, cost, and risk of drug interactions. Switching may correct PI/r-dependent (but not other) dyslipidaemias, but also carries the possibility of losing virological control.[10, 11] Either strategy may introduce new adverse events (e.g. myopathy with statins or with raltegravir).

Ultimately, intervening for hypercholesterolaemia will be of clinical relevance only if those being treated have elevated cardiovascular risk.[11] Although both statin therapy and PI/r switching lower total and non-HDL cholesterol and triglyceride levels,[10, 12-14] only one randomised study has compared the two approaches.[15] In that study, pravastatin was more effective than PI/r switching for reducing lipid levels over a 12-month period; cardiovascular risk reduction, however, was not an endpoint. However, more potent statins are now available and most of the PIs in the aforementioned study (nelfinavir, indinavir/ritonavir, saquinavir/ritonavir, amprenavir/ritonavir) have been superseded. There are also more lipid-neutral switch options available in the form of integrase strand transfer inhibitors.

Thus for contemporary drugs, the optimal strategy for treating hypercholesterolaemia in HIV infection is unclear, and remains an important clinical dilemma. Despite the limited evidence, 2014 European AIDS Clinical Society (EACS) guidelines recommend PI/r switching above lipid-lowering therapies, whereas United States guidelines for HIV dyslipidaemia, last updated in 2003, suggest only that clinicians decide between the two on a case-by-case basis. Here, we report the results of the Statin or Switch (SoS) trial, a 12-week study to assess the efficacy and safety of rosuvastatin versus PI/r switching for the treatment of fasting hypercholesterolaemia in HIV-infected adults with increased cardiovascular risk. It was hypothesised that rosuvastatin would result in greater reductions in fasting total cholesterol than PI/r switching.

Methods

Study participants

HIV-1-infected adults (age ≥18 years) were eligible if they were on combination antiretroviral therapy (cART) including a PI/r, with a plasma viral load of <50 copies/mL (both for at least six months prior to screening), and had a fasting total cholesterol ≥5.5 mmol/L, elevated cardiovascular risk (Framingham score ≥8% at 10 years,[16] diabetes mellitus, or family history of premature coronary artery disease in a first-degree relative[17]), at least one virologically-effective PI/r switch option, had not received lipid-lowering therapy in the previous three months nor required immediate statin therapy, and had no contraindications to statin therapy. Patients who were pregnant, breastfeeding or attempting to fall pregnant were ineligible. All participants provided written, informed consent.

Study design and randomisation

This was a 12-week, randomised, open-label study conducted at nine sites in Australia and Spain, in accordance with the Helsinki II Declaration and the International Conference on Harmonisation Good Clinical Practice Guidelines. The study was approved by local ethics committees, and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12612000732886), and with ClinicalTrials.gov (NCT01935674).

Participants were randomly assigned in a 1:1 ratio, either to PI/r switching, or to receive rosuvastatin 10 mg/day (the maximum dose recommended for use with a PI/r), lowered to 5 mg/day in participants of Asian ethnicity.[18] Switch options were based upon anticipated lipid effect and antiretroviral potency; raltegravir and rilpivirine were recommended PI/r switch options, [7, 19, 20] as was unboosted atazanavir.[19, 21] Additional switch options were considered on an individual basis. Efavirenz was not recommended, due to its known dyslipidaemic effects.[22] Standardised dietary and exercise advice was provided to all participants. As the effect of a switch from earlier PI/rs such as lopinavir/ritonavir resulted in greater reduction in fasting lipids compared with atazanavir/ritonavir ,[14] participants were stratified by the PI/r at study entry (atazanavir/ritonavir vs. other), and according to the screening fasting total cholesterol (>7.0 mmol/L vs. ≤7.0 mmol/L), with permuted blocks of six used for randomisation.

Study visits occurred at weeks 0, 4 and 12. The study duration was based on that of pivotal trials for rosuvastatin and other statin drugs.[18] At each visit, blood samples were obtained for measurement of cholesterol fractions (total, LDL, VLDL, HDL), triglycerides, glucose, and insulin after a 12-hour overnight fast. Cardiovascular risk was estimated with the Framingham and D:A:D risk scores at enrolment and at week 12.[23, 24] Estimated insulin resistance and pancreatic β-cell insulin secretion were calculated using the homeostasis model assessment (HOMA) equations.[25] Quality-of-life was assessed using a validated patient-reported health survey (SF-12®, OptumInsight Inc., Eden Prairie, MN, USA). Measurements of LDL particle size by nuclear magnetic resonance spectroscopy (LipoScience Inc., Raleigh, NC, USA), and of D-dimer (VIDAS®, bioMérieux, Marcy l'Etoile, France) were performed at centralised laboratories.

Adverse events were assessed via history, physical examination, and laboratory testing. Concomitant medications and immunovirological parameters (CD4+ lymphocyte counts, plasma viral load) were assessed throughout the study.

Endpoints, sample size calculation and statistical analysis

The primary objective was to compare the percentage change from week 0 to week 12 in fasting total cholesterol between the rosuvastatin and PI/r switch groups. Secondary endpoints included the changes in: other fasting lipid parameters (cholesterol fractions, triglycerides); Framingham and D:A:D risk scores; fasting glucose, insulin, HOMA (IR, β); D-dimer; LDL particle size; quality-of-life scores; and adverse events. Pre-planned subgroup analyses of the primary endpoint were performed according to the randomisation strata (screening fasting total cholesterol >7.0 mmol/L vs. ≤7.0 mmol/L; atazanavir/ritonavir vs. other PI/r). As the current preferred PI/r options (atazanavir/ritonavir, once-daily darunavir/ritonavir) appear to have similar effects upon total cholesterol,[7] an additional post hoc analysis of the primary endpoint was performed for preferred vs. non-preferred PI/rs.[5] All analyses were intention-to-treat. Adverse events were graded according to the 2004 Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events,[26] and assigned causality.

In published cholesterol-lowering treatment studies in HIV-infected adults, reductions in total cholesterol of 28% were reported with rosuvastatin 10 mg/day (standard deviation [SD] 18),[13] while switching lopinavir/ritonavir to raltegravir result in a 13% reduction (SD unreported).[10] Switching from various PI/rs to raltegravir led to relative reductions in total cholesterol of between 3% (for atazanavir/ritonavir) and 17% (for lopinavir/ritonavir).[14] These data suggest an absolute difference between rosuvastatin and lopinavir/ritonavir switching of approximately 15%.

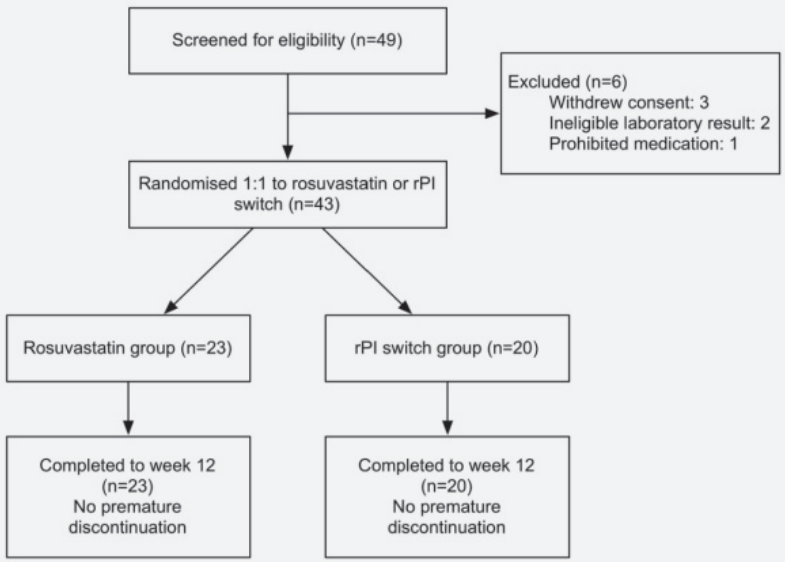
Using 1:1 randomisation, to permit rejection of the null hypothesis (i.e. mean changes in the experimental and control groups are similar) with an α of 0.05 and 80% power, the sample size was 24 per group, if all participants were on lopinavir/ritonavir at study entry. If 50% of participants were on lopinavir/ritonavir, and 50% were on atazanavir/ritonavir, the between-group difference for total cholesterol would be expected to be larger (estimated 20%), giving a sample size of 14 per group for an SD of 20. The effects of darunavir/ritonavir and fosamprenavir/ritonavir on total cholesterol levels appear similar to those of lopinavir/ritonavir,[27] and so were not expected to affect the required sample size. To allow for non-parametric distribution of changes from baseline and a loss to follow-up of 10%, the maximum sample size was set at 30 participants per group.

The Wilcoxon rank-sum test was used for between-group comparisons of primary and secondary endpoints. Analysis of variation (ANOVA) was used to assess change in total cholesterol against intervention type, baseline total cholesterol (as continuous and categorical variables), and the PI/r at study entry. Differences in adverse event rates were evaluated using the *chi*-square test.

Results

Between June 2012 and April 2014, 49 individuals were screened; six were ineligible or withdrew consent (**Figure 1**). Although below the original target of 60, all 43 randomised participants (23 rosuvastatin, 20 PI/r switch) adhered to their allocated intervention, reaching study completion (week 12); 22 (51%) were on lopinavir/ritonavir at study entry, reducing the required number of participants.

Figure 1. Study profile and participant disposition



PI/r, ritonavir-boosted protease inhibitor.

Baseline characteristics were similar between the two groups (**Table 1**): 42 (98%) were men, 41 (95%) were of white race, and 20 (47%) were current smokers. The mean total cholesterol

was 6.2 mmol/L (SD 1.2). Three PI/r drugs were used at enrolment – lopinavir/ritonavir (51%), atazanavir/ritonavir (28%), and darunavir/ritonavir (11%). One participant took darunavir/ritonavir twice-daily. Within the PI/r switch group, raltegravir (45%) and rilpivirine (20%) were the most common PI/r substitutions.

Table 1. Baseline characteristics

	Rosuvastatin (n=23)	PI/r switch (n=20)	Total (n=43)
Male, n (%)	22 (96)	20 (100)	42 (98)
Mean age, years	53 (8.7)	56 (8.2)	55 (8.5)
Race, n (%)			
White	22 (96)	19 (95)	41 (95)
Black	0 (0)	0 (0)	0 (0)
Other	1 (5)	1 (5)	2 (5)
Smoking status, n (%)			
Current	12 (52)	8 (40)	20 (47)
Former	9 (39)	6 (30)	15 (35)
Never	2 (9)	6 (30)	8 (19)
Diabetes mellitus, n (%)	0 (0)	0 (0)	0 (0)
Family history premature CVD, n (%)	1 (4)	1 (5)	2 (5)
Cardiovascular risk score			
Framingham, 10 years	13.5 (5.8)	13.8 (4.3)	13.6 (5.1)
D:A:D, 5 years	8.5 (4.1)	8.3 (5.2)	8.4 (4.6)
NRTI backbone at study entry, n (%)			
tenofovir-emtricitabine	10 (43)	9 (45)	19 (44)
abacavir-lamivudine	6 (26)	4 (20)	10 (23)
single NRTI	2 (9)	1 (5)	2 (5)
nil (NRTI-sparing regimen)	4 (17)	6 (30)	9 (21)
PI/r at study entry, n (%)			
lopinavir/ritonavir BD	12 (52)	10 (50)	22 (51)
atazanavir/ritonavir QD	7 (30)	5 (25)	12 (28)
darunavir/ritonavir QD	4 (17)	4 (20)	8 (9)
darunavir/ritonavir BD	0 (0)	1 (5)	1 (2)
Pre-selected PI/r switch, n (%)			
Raltegravir	-	9 (45)	-
Rilpivirine	-	4 (20)	-
atazanavir (unboosted)	-	3 (16)	-
elvitegravir/cobicistat	-	1 (5)	
≥2 antiretroviral drugs	-	3 (16)*	
Weight, kg	79 (12)	78 (18)	78 (15)
Body-mass index, kg/m²	25.7 (2.8)	25.7 (5.3)	25.7 (4.1)
Systolic blood pressure, mmHg	130 (15)	134 (14)	132 (15)
Diastolic blood pressure, mmHg	80 (11)	83 (7.7)	82 (9.6)
Lipids			

total cholesterol, mmol/L	6.3 (1.4)	6.0 (0.9)	6.2 (1.2)
HDL cholesterol, mmol/L	1.1 (0.2)	1.3 (0.4)	1.2 (0.3)
LDL cholesterol, mmol/L	4.1 (0.9)	3.8 (0.8)	4.0 (0.9)
VLDL cholesterol, mmol/L	1.2 (1.4)	1.0 (0.5)	1.1 (1.1)
triglycerides, mmol/L	2.3 (1.4)	2.2 (1.1)	2.2 (1.3)
total:HDL cholesterol ratio	5.7 (1.7)	4.8 (1.0)	5.3 (1.4)
Total cholesterol, n (%)			
≤7.0 mmol/L	18 (78)	17 (85)	35 (81)
>7.0 mmol/L	5 (22)	3 (15)	8 (19)
Glycaemic parameters			
glucose, mmol/L	5.2 (0.6)	5.2 (0.5)	5.2 (0.5)
insulin, mU/L	14 (10)	14 (10)	14 (10)
HOMA-IR, mmol.mU/L²	3.1 (2.2)	3.3 (2.7)	3.2 (2.4)
HOMA-β, %	200.1 (274.5)	173.9 (124.5)	188.6 (219.6)
Biochemistry			
creatinine, µmol/L	85 (13)	80 (20)	82 (16)
total bilirubin, µmol/L	19 (15)	18 (15)	19 (15)
alanine aminotransferase, U/L	31 (16)	32 (21)	31 (18)
aspartate aminotransferase, U/L	27 (15)	25 (7.7)	26 (12)
alkaline phosphatase, U/L	152 (76)	124 (72)	139 (74)
gamma-glutamyl transferase, U/L	36 (26)	48 (60)	41 (45)
creatine kinase, U/L	222 (415)	149 (12)	188 (313)
Haematology			
haemoglobin, g/L	153 (14)	145 (11)	149 (13)
CD4+ lymphocyte percentage, %	29 (7.9)	31 (9.1)	30 (8.4)
CD4+ lymphocyte count, x 10^6/L	632 (334)	579 (238)	606 (289)

All values are mean (SD), except where stated as n (%). All laboratory values are fasting.

* PI/r switches were: darunavir/ritonavir and raltegravir replaced with lamivudine, etravirine and raltegravir (n=1); lopinavir/ritonavir monotherapy replaced with tenofovir, emtricitabine and rilpivirine (n=1); lopinavir/ritonavir and lamivudine replaced with tenofovir, emtricitabine and rilpivirine (n=1).

BD, twice-daily; CVD, cardiovascular disease; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment – insulin resistance; HOMA-β, homeostasis model assessment – β-cell function; LDL, low-density lipoprotein cholesterol; NRTI, nucleos(t)ide reverse transcriptase inhibitor; QD, once-daily; PI/r, ritonavir-boosted protease inhibitor; SD, standard deviation; VLDL, very low-density lipoprotein cholesterol.

At week 12, the mean fasting total cholesterol fell by 1.4 mmol/L with rosuvastatin, significantly more than the 0.6 mmol/L reduction seen in the PI/r group (-21.4% [SD 19.2] vs. -8.7% [SD 10.8], respectively); a relative difference of 12.7% (95% confidence interval [CI] 2.9, 22.5; p=0.003) (**Figure 2**, **Table 2**). Similar between-group differences were observed at week 12 for LDL cholesterol (-29.9% [SD 27.3] vs. -1.0% [SD 20.0], respectively; difference 28.9% [95% CI 12.0, 43.8]; p<0.001), and the total:HDL cholesterol ratio (-22.7% [SD 18.3] vs. -7.6% [SD 14.1], respectively; difference 15.1% [95% CI 4.9, 25.3]; p=0.002). Decreases in triglycerides and VLDL cholesterol, however, were significantly greater in the PI/r switch group. For all the aforementioned endpoints, between-group differences were also

significant by week 4, with minimal change evident from week 4 to week 12. The between-group difference in the change in HDL cholesterol at each time point was non-significant, as was the change in LDL particle size at week 12.

Table 2. Change in primary and secondary endpoints

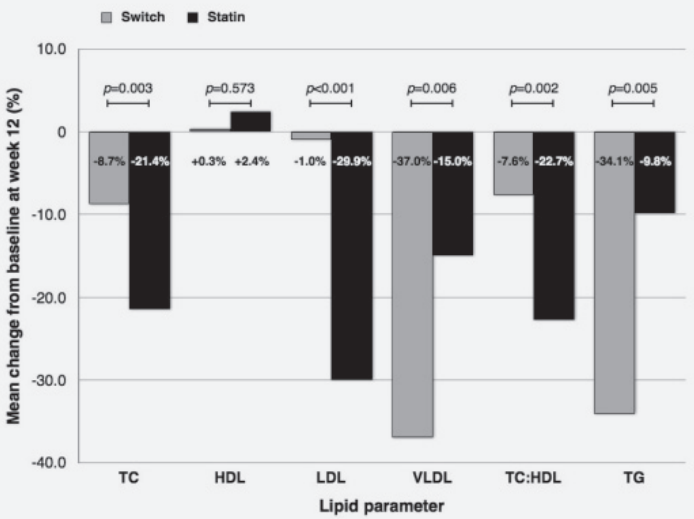
	Week	Rosuvastatin	PI/r switch	Difference (95% CI)	*p*
Total cholesterol	4	-24.1 (11.8)	-7.3 (10.3)	16.8 (9.7, 23.9)	<0.001
	12	-21.4 (19.2)	-8.7 (10.8)	12.7 (2.9, 22.5)	0.003
HDL cholesterol	4	-1.3 (13.2)	+3.3 (14.5)	4.6 (-4.1, 13.4)	0.377
	12	+2.4 (12.1)	+0.3 (15.0)	2.2 (-10.5, 6.2)	0.574
LDL cholesterol	4	-34.9 (12.3)	-3.5 (19.3)	31.3 (21.3, 41.4)	<0.001
	12	-29.9 (27.3)	-1.0 (20.0)	28.9 (14.0, 43.8)	<0.001
VLDL cholesterol	4	-0.3 (35.1)	-31.2 (30.3)	31.0 (9.9, 52.0)	0.004
	12	-15.0 (26.6)	-37.0 (25.3)	22.1 (6.0, 38.1)	0.006
TC:HDL cholesterol ratio	4	-21.7 (16.2)	-8.8 (15.3)	12.9 (2.9, 23.0)	0.009
	12	-22.7 (18.3)	-7.6 (14.1)	15.1 (4.9, 25.3)	0.002
Triglycerides	4	+1.6 (33.5)	-25.7 (40.0)	27.2 (4.0, 50.5)	0.008
	12	-9.8 (31.7)	-34.1 (28.0)	24.3 (5.7, 42.8)	0.005
LDL particle size	12	+0.2 (2.8)	+0.8 (3.7)	0.7 (-1.3, 2.8)	0.592
Glucose	12	-2.1 (13.0)	+3.0 (9.9)	5.1 (-2.1, 12.4)	0.113
Insulin	12	+14.7 (59.3)	-6.4 (40.3)	21.1 (-54.6, 12.4)	0.338
D-dimer	12	-3.7 (35.7)	-4.5 (46.9)	0.9 (-26.7, 25.0)	0.890
Weight	12	-0.3 (2.8)	+0.8 (3.3)	1.1 (-0.7, 3.0)	0.427
Body-mass index	12	-0.3 (2.8)	+0.8 (3.3)	1.1 (-0.7, 3.0)	0.420
HOMA-IR	12	-0.4 (2.2)	-0.4 (1.5)	<0.1 (-1.2, 1.2)	0.612
HOMA-β	12	+34.1 (365.2)	-29.5 (105.0)	63.6 (-244.3, 117.2)	0.046
Quality-of-life (SF-12®)	12	+0.4 (8.0)	+2.2 (7.8)	1.1 (-0.9, 3.1)	0.098
Framingham, % at 10 years*	12	-3.4 (5.9)	-2.1 (2.7)	1.4 (-1.5, 4.3)	0.080
D:A:D, % at 5 years*	12	-1.6 (3.2)	-0.5 (3.1)	1.1 (-0.9, 3.1)	0.098

All values are the mean percentage change (SD) in fasting measurements from week 0, unless otherwise stated.* Change in cardiovascular risk scores reported as absolute changes. 95% CI, 95% confidence interval; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment – insulin resistance; HOMA-β, homeostasis model assessment – β-cell function; LDL, low-density lipoprotein cholesterol; PI/r, ritonavir-boosted protease inhibitor; SD, standard deviation; VLDL, very low-density lipoprotein cholesterol.

By ANOVA, rosuvastatin use was associated with an 11.6% greater decline in total cholesterol at week 12 than PI/r switch (95% CI 2.6, 20.6; p=0.013). The reduction in total cholesterol was also greater for higher baseline values, regardless of whether it was treated as a categorical or continuous variable; each 1 mmol/L increase in baseline total cholesterol predicted a 4.8% greater decline at week 12 (95% CI 5.3, 28.5; p=0.005). The adjusted coefficient of variation (r^2) for this model was 26.5%, and there was no significant interaction between the intervention type and baseline fasting total cholesterol level (p=0.319), indicating that these were independent associations.

Rosuvastatin was more effective at lowering total cholesterol than PI/r switching when the PI/r at study entry was atazanavir/ritonavir (**Table 3**). Amongst non-atazanavir PI/rs (lopinavir/ritonavir, darunavir/ritonavir), rosuvastatin remained numerically more effective, but non-significantly (p=0.063). In the post hoc analysis, rosuvastatin remained superior to PI/r switching for currently preferred PI/rs, but not non-preferred PI/rs.

Figure 2. Proportional changes from baseline of fasting lipid parameters at week 12



HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein cholesterol.

Table 3. Subgroup analyses

Change in fasting total cholesterol by baseline total cholesterol, % (SD)				
	n	**≤7.0 mmol/L**	**n**	**>7.0 mmol/L**
Rosuvastatin	18	-16.7 (19.1)	5	-38.3 (5.1)
PI/r switch	17	-7.2 (11.1)	3	-16.9 (2.5)
Difference (95% CI)		9.5 (0.3, 20.3)		21.3 (13.5, 29.2)
p		0.021		0.025
Change in fasting total cholesterol by entry PI/r: atazanavir/ritonavir vs. other PI/r, % (SD)				
	n	**Ritonavir/atazanavir**	**n**	**Other PI/r**
Rosuvastatin	7	-27.6 (9.5)	16	-18.7 (21.8)
PI/r switch	5	-8.1 (10.1)	15	-8.9 (11.3)
Difference (95% CI)		19.5 (6.7, 32.2)		9.8 (-3.1, 22.8)
p		0.007		0.063

Change in fasting total cholesterol by entry PI/r: preferred vs. non-preferred PI/r, % (SD)*				
	n	Preferred PI/r	n	Non-Preferred PI/r
Rosuvastatin	11	-28.8 (11.0)	12	-14.6 (22.8)
PI/r switch	9	-7.4 (10.4)	11	-9.7 (11.5)
Difference (95% CI)		21.3 (11.2, 31.5)		4.9 (-11.0, 20.9)
p		0.001		0.325

* Post hoc analysis of preferred vs. non-preferred PI/rs, as designated by the United States Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, updated May 1, 2014. Preferred PI/rs: atazanavir/ritonavir (n=12), once-daily darunavir/ritonavir (n=8); non-preferred PI/rs: twice-daily lopinavir/ritonavir (n=22), twice-daily darunavir/ritonavir (n=1).
CI, confidence interval; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein; PI/r, ritonavir-boosted protease inhibitor; SD, standard deviation; VLDL, very low-density lipoprotein.

Mean absolute cardiovascular risk reduction was non-significantly higher with rosuvastatin than PI/r switching (Framingham: -3.4% vs. -2.1%, respectively, p=0.080; D:A:D: -1.6% vs. -0.5%, respectively, p=0.098). These changes were not due to other modifiable risk factors; during the study period, systolic and diastolic blood pressures remained similar in both groups, and no participant altered his/her smoking status.

Estimated insulin secretion (HOMA-β) at week 12 increased with rosuvastatin, and fell with PI/r switching (+34.1% [SD 365.2] vs. -29.5% [SD 105.0], respectively, p=0.046). Between-group changes in fasting insulin, glucose, and estimated insulin resistance (HOMA-IR) were similar. There were no incident cases of diabetes mellitus. The between-group difference for changes in the D-dimer and LDL particle size were non-significant.

Most participants (65%) experienced at least one clinical adverse event (**Table 4**). More drug-related events were observed in the PI/r switch group (10 events vs. 1 event, p=0.001); most were gastrointestinal (nausea, diarrhoea), and of mild or moderate severity (DAIDS grade 1 or 2). One serious adverse event, unrelated to study drug or procedures, occurred in each group. There were no instances of myalgia or myopathy, grade 3 or 4 laboratory adverse events, or premature discontinuation from study, and the quality-of-life assessments were similar between the groups.

Table 4. Treatment-emergent clinical adverse events

	Rosuvastatin (n=23)	PI/r switch (n=20)
One or more events, n (%)	14 (61)	14 (70)
Drug-related events, n (%)*	1 (4)	10 (50)
Nausea	1 (4)	4 (20)
Diarrhoea	0 (0)	4 (20)
Fatigue	0 (0)	2 (10)
myalgia/myopathy	0 (0)	0 (0)
Rash	0 (0)	1 (5)
Other	1 (4)	6 (30)
Serious adverse event – all, n (%)†	1 (4)	1 (5)

Serious adverse event – study drug-related, n (%)	0 (0)	0 (0)
Discontinuation due to adverse event, n (%)	0 (0)	0 (0)

* p=0.001, by *chi*-square test.
† Rosuvastatin group: unstable angina requiring coronary artery stenting; PI/r switch group: tibial fracture.

One participant assigned to rosuvastatin experienced loss of virological suppression; the plasma viral load measured 360 copies/mL at week 12, but returned to <50 copies/mL three months later without change to cART regimen or rosuvastatin. The viral rebound was adjudged to be secondary to suboptimal cART adherence.

Discussion

In this randomised study of the treatment of hypercholesterolaemia in adults with increased cardiovascular risk receiving a PI/r, both rosuvastatin and PI/r switching yielded decreases in total and LDL cholesterol by week 4 that were maintained through to week 12. The reductions were larger, and associated with fewer adverse events for the rosuvastatin 10 mg/day intervention than for PI/r switching, although tolerability did not affect study completion rates. Subgroup analyses revealed rosuvastatin was more effective than PI/r switching at all levels of hypercholesterolaemia, but with differential effects based on the PI/r taken.

Reductions in total and LDL cholesterol in the rosuvastatin group were comparable to those observed with rosuvastatin therapy in other HIV-infected cohorts.[13, 28] Likewise, compared to earlier PI/r switch studies,[10, 14, 21, 29] total cholesterol, LDL cholesterol and triglyceride reductions achieved within the PI/r switch group in this study were similar. It should be noted, however, that none of these previous clinical trials, including those switch studies with pharmaceutical sponsorship, targeted exclusively participants with clinically elevated cardiovascular risk.

The results concur with those of the only prior study to compare a statin (pravastatin) with PI/r switching.[15] However, this earlier study used efavirenz as a switch option, despite its known lipid effects,[22] and also used the less potent pravastatin.[13] Results of the post hoc subgroup analysis suggest that PI/r switching for the sole purpose of reducing lipids may be unwarranted if the patient is on a current preferred PI/r (atazanavir/ritonavir, once-daily darunavir/ritonavir). The corollary is that as progressively fewer patients are commenced on non-preferred PI/rs such as lopinavir/ritonavir as initial antiretroviral therapy, PI/r switching as a lipid-lowering strategy is likely to become less clinically relevant. This would leave statin therapy as the intervention of choice for hypercholesterolaemia for the majority of adults receiving a PI/r, although this adds to daily pill count, to the potential detriment of cART adherence. This is at odds with the recommendations of the 2014 EACS antiretroviral guidelines, which continues to place PI/r switching above lipid-lowering drugs in the treatment approach to dyslipidaemia.

The observed lipid changes in this study were insufficient to effect a significant between-group difference for either the Framingham or D:A:D scores; the mean scores nevertheless fell from baseline with either intervention. While it may be posited that a larger sample size may have detected a greater between-group difference in risk scores, that the lipid changes plateaued after week 4 suggests that this is unlikely to be the case. These falls in risk scores are, in fact, in keeping with the results of recent meta-analyses of statin trials, which indicate that lipid reduction alone produces modest decreases in cardiovascular morbidity/mortality in a primary prevention setting.[9, 30] However, statin therapy has also been demonstrated to significantly reduce the volume of non-calcified coronary artery plaque volume compared to placebo in HIV-infected patients, a finding yet to be reported for PI/r switching, and a reminder that risk score assessments are algorithm-derived; only a much larger and longer clinical endpoint study in a more diverse population might provide a better assessment of the actual clinical effect.

The dose of rosuvastatin is another variable influencing risk reduction and lipid-lowering efficacy. Our study used 10 mg/day, the maximum recommended dose for co-administration with PI/rs.[18] In contrast, the JUPITER study reported significantly lower cardiovascular event incidence using rosuvastatin 20 mg/day.[31] This was, however, compared to a placebo group, not an active second intervention. Furthermore, rosuvastatin is affected by PI/r interactions that inhibit rosuvastatin metabolism, increasing mean exposure by 1.5-, 2-, and 3-fold with concomitant twice-daily darunavir/ritonavir, twice-daily lopinavir/ritonavir, and once-daily atazanavir/ritonavir, respectively.[18] Thus, the effective dose employed in our study would likely have at least equalled that of 20 mg/day in the absence of a PI/r, and possibly even higher for participants on atazanavir/ritonavir. This interaction could explain why PI/r switching appears to be similar in efficacy to rosuvastatin for the non-atazanavir/ritonavir PI/r subgroup, although the ritonavir dose, which is higher with lopinavir/ritonavir than once-daily PI/r regimens (200 mg/day vs. 100 mg/day), may also play a role. The small cohort size means that the power to resolve this question is lacking in this study. Studies comparing different PI/rs and different ritonavir doses would be required to answer this question.

Despite pharmacokinetic boosting, only one rosuvastatin-related adverse event was recorded (DAIDS grade 1 nausea). Pravastatin, in contrast, does not require dose adjustment with PI/rs, but is inferior to both rosuvastatin and pitavastatin in HIV-infected patients for reducing total and LDL cholesterol.[13, 32] At the time of writing, pitavastatin is not routinely available in Australia or Europe, but appears to have minimal interactions with PI/rs,[33, 34] and may merit further study as an alternative to rosuvastatin .

The significantly greater estimated insulin secretion with rosuvastatin at week 12 was an unexpected finding, but was unaccompanied by significant between-group differences in body weight, fasting glucose, insulin or the estimated insulin resistance (HOMA-IR). Rosuvastatin (versus placebo) has been associated with a higher incidence of diabetes mellitus in the JUPITER study over a median of two years.[31] However, the risk appears to be limited to those patients already at relatively high risk for developing diabetes (e.g. concomitant obesity/metabolic syndrome, elevated glycosylated haemoglobin).[35] The

mechanism is unknown, and the few studies examining the effect of rosuvastatin on insulin resistance parameters have given inconsistent results.[36, 37] As our study was only 12 weeks' duration, the clinical relevance of this result is unknown, although a true, early diabetogenic effect cannot be excluded. Both interventions showed minimal changes in both the D-dimer and LDL particle size; a longer follow-up may reveal progressively larger changes and significant between-group differences.

A number of limitations to this study should be noted. The cohort size was small, and the follow-up period of 12 weeks was short, although sufficient to identify significant and stable differences in the primary endpoint, vindicating the original sample size calculations and study duration. The population was homogeneous, and the findings are thus specific for white men receiving PI/rs. For instance, rosuvastatin requires further dose reductions in patients of Asian ethnicity,[18] which may give different outcomes. The PI/r switch options were also regarded as equivalent, an assumption yet to be confirmed with a randomised trial. Also, dual intervention (rosuvastatin and PI/r switching together), which may be more potent than either strategy separately, was not tested in this study. Despite standardised dietary and exercise advice being given, it is possible that one group may have adhered to these recommendations more stringently. However, mean body weight (and hence body-mass index) changed by <1% from baseline in both groups, suggesting that this was unlikely.

In conclusion, rosuvastatin was superior to PI/r switching overall, an advantage most apparent amongst participants receiving a preferred PI/r.

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References

1. Periard D, Telenti A, Sudre P, Cheseaux JJ, Halfon P, Reymond MJ, et al. Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. The Swiss HIV Cohort Study. Circulation. 1999; **100**(7): 700-5.

2. Mulligan K, Grunfeld C, Tai VW, Algren H, Pang M, Chernoff DN, et al. Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. J Acquir Immune Defic Syndr. 2000; **23**(1): 35-43.

3. Friis-Moller N, Reiss P, Sabin CA, Weber R, Monforte A, El-Sadr W, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med. 2007; **356**(17): 1723-35.
4. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis. 2010; **201**(3): 318-30.
5. Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Rockville, Maryland, USA: Department of Health and Human Services; 2014 [updated May 1].
6. Monforte A, Reiss P, Ryom L, El-Sadr W, Dabis F, De Wit S, et al. Atazanavir is not associated with an increased risk of cardio or cerebrovascular disease events. Aids. 2013; **27**(3): 407-15.
7. Lennox JL, Landovitz RJ, Ribaudo HJ, Ofotokun I, Na LH, Godfrey C, et al. Efficacy and Tolerability of 3 Nonnucleoside Reverse Transcriptase Inhibitor-Sparing Antiretroviral Regimens for Treatment-Naive Volunteers Infected With HIV-1: A Randomized, Controlled Equivalence Trial. Ann Intern Med. 2014; **161**(7): 461-71.
8. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. Jama. 1999; **282**(24): 2340-6.
9. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, et al. Statins for the primary prevention of cardiovascular disease. The Cochrane database of systematic reviews. 2013; **1**: CD004816.
10. Eron JJ, Young B, Cooper DA, Youle M, Dejesus E, Andrade-Villanueva J, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. Lancet. 2010; **375**(9712): 396-407.
11. Carr A, Hoy J, Pozniak A. The ethics of switch/simplify in antiretroviral trials: non-inferior or just inferior? PLoS Med. 2012; **9**(7): e1001240.
12. Silverberg MJ, Leyden W, Hurley L, Go AS, Quesenberry CP, Jr., Klein D, et al. Response to newly prescribed lipid-lowering therapy in patients with and without HIV infection. Ann Intern Med. 2009; **150**(5): 301-13.
13. Aslangul E, Assoumou L, Bittar R, Valantin MA, Kalmykova O, Peytavin G, et al. Rosuvastatin versus pravastatin in dyslipidemic HIV-1-infected patients receiving protease inhibitors: a randomized trial. Aids. 2010; **24**(1): 77-83.
14. Martinez E, Larrousse M, Llibre JM, Gutierrez F, Saumoy M, Antela A, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. Aids. 2010; **24**(11): 1697-707.
15. Calza L, Manfredi R, Colangeli V, Tampellini L, Sebastiani T, Pocaterra D, et al. Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidaemia. Aids. 2005; **19**(10): 1051-8.
16. Law MG, Friis-Moller N, El-Sadr WM, Weber R, Reiss P, D'Arminio Monforte A, et al. The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. HIV Med. 2006; **7**(4): 218-30.
17. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). Jama. 2001; **285**(19): 2486-97.
18. FDA Crestor Prescribing Information. 2014 [updated July 08].
19. Malan DR, Krantz E, David N, Wirtz V, Hammond J, McGrath D. Efficacy and safety of atazanavir, with or without ritonavir, as part of once-daily highly active antiretroviral

therapy regimens in antiretroviral-naive patients. J Acquir Immune Defic Syndr. 2008; **47**(2): 161-7.
20. Tebas P, Sension M, Arribas J, Duiculescu D, Florence E, Hung CC, et al. Lipid levels and changes in body fat distribution in treatment-naive, HIV-1-Infected adults treated with rilpivirine or Efavirenz for 96 weeks in the ECHO and THRIVE trials. Clin Infect Dis. 2014; **59**(3): 425-34.
21. Sension M, Andrade Neto JL, Grinsztejn B, Molina JM, Zavala I, Gonzalez-Garcia J, et al. Improvement in lipid profiles in antiretroviral-experienced HIV-positive patients with hyperlipidemia after a switch to unboosted atazanavir. J Acquir Immune Defic Syndr. 2009; **51**(2): 153-62.
22. van Leth F, Phanuphak P, Stroes E, Gazzard B, Cahn P, Raffi F, et al. Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naive patients infected with HIV-1. PLoS Med. 2004; **1**(1): e19.
23. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008; **117**(6): 743-53.
24. Friis-Moller N, Thiebaut R, Reiss P, Weber R, Monforte AD, De Wit S, et al. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. Eur J Cardiovasc Prev Rehabil. 2010; **17**(5): 491-501.
25. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; **28**(7): 412-9.
26. Division of AIDS Table for Grading the severity of Adult and Pediatric Adverse events. 2004 December 2004 [cited; Available from: http://rs.tech-res.com/safetyandpharmacovigilence/
27. Ortiz R, Dejesus E, Khanlou H, Voronin E, van Lunzen J, Andrade-Villanueva J, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. Aids. 2008; **22**(12): 1389-97.
28. Eckard AR, Jiang Y, Debanne SM, Funderburg NT, McComsey GA. Effect of 24 weeks of statin therapy on systemic and vascular inflammation in HIV-infected subjects receiving antiretroviral therapy. J Infect Dis. 2014; **209**(8): 1156-64.
29. Palella FJ, Jr., Fisher M, Tebas P, Gazzard B, Ruane P, Van Lunzen J, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. Aids. 2014; **28**(3): 335-44.
30. Ray KK, Seshasai SR, Erqou S, Sever P, Jukema JW, Ford I, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. Arch Intern Med. 2010; **170**(12): 1024-31.
31. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008; **359**(21): 2195-207.
32. Sponseller CA, Kryzhanovski VA, Morgan RE, Campbell SE, Thompson MA, Aberg JA. After 52 weeks, pitavastatin is superior to pravastatin for LDL-C lowering in patients with HIV. 21st Conference on Retroviruses and Opportunistic Infections. Boston, MA, USA; March 3 - 6, 2014.
33. Morgan RE, Campbell SE, Suehira K, Sponseller CA, Yu CY, Medlock MM. Effects of steady-state lopinavir/ritonavir on the pharmacokinetics of pitavastatin in healthy adult volunteers. J Acquir Immune Defic Syndr. 2012; **60**(2): 158-64.

34. Yu CY, Campbell SE, Sponseller CA, Small DS, Medlock MM, Morgan RE. Steady-state pharmacokinetics of darunavir/ritonavir and pitavastatin when co-administered to healthy adult volunteers. Clin Drug Investig. 2014; **34**(7): 475-82.
35. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet. 2012; **380**(9841): 565-71.
36. Sharif A, Ravindran V, Moore R, Dunseath G, Luzio S, Owens D, et al. The effect of rosuvastatin on insulin sensitivity and pancreatic beta-cell function in nondiabetic renal transplant recipients. Am J Transplant. 2009; **9**(6): 1439-45.
37. Kostapanos MS, Milionis HJ, Agouridis AD, Rizos CV, Elisaf MS. Rosuvastatin treatment is associated with an increase in insulin resistance in hyperlipidaemic patients with impaired fasting glucose. Int J Clin Pract. 2009; **63**(9): 1308-13.

ARTICLE 5

Dual therapy with etravirine plus raltegravir for virologically suppressed HIV-infected patients: a pilot study.

Polyana Monteiro, Iñaki Perez, Montserrat Laguno, Maria Martínez-Rebollar, Ana González-Cordon, Montserrat Lonca, Josep Mallolas, Jose L. Blanco, Jose M. Gatell and Esteban Martínez.

Infectious Diseases Unit, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona.

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Dual therapy with etravirine plus raltegravir for virologically suppressed HIV-infected patients: a pilot study

Polyana Monteiro*, Iñaki Perez, Montserrat Laguno, Maria Martínez-Rebollar, Ana González-Cordon, Montserrat Lonca, Josep Mallolas, Jose L. Blanco, Jose M. Gatell and Esteban Martínez

Infectious Diseases Unit, Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain

*Corresponding author. Tel: +34-93-227-55-74; Fax: +34-93-451-44-38; E-mail: polymonteiro@hotmail.com

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Background: Clinical use of protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs) may be hampered by toxicity, interactions or resistance issues. Simple and effective antiretroviral regimens avoiding both drug classes may be needed for selected patients.

Methods: This was a prospective cohort study. Virologically suppressed patients on PI or NRTI regimens, with problems of tolerability, safety concerns due to comorbidities or risk of drug interactions for both PIs and NRTIs, were given the opportunity to switch their regimen to etravirine plus raltegravir. Patients were required not to have prior virological failure to raltegravir and if there was prior non-nucleoside reverse transcriptase inhibitor (NNRTI) virological failure, only patients in whom efficacy of etravirine could be anticipated through the Stanford Drug Resistance Database were included. Follow-up was scheduled for at least 48 weeks, unless the patient was lost to follow-up or discontinued therapy.

Results: Twenty-five patients were included. Their median age was 54 years; they had a median of 16 years on antiretroviral therapy and a median of nine previous regimens; 21 (84%) patients had previous virological failure; and 15 (60%) patients had a genotypic test that showed three or more NRTI mutations in 9 (36%), four or more PI mutations in 11 (44%) and at least one NNRTI mutation in 8 (32%) patients. At 48 weeks efficacy was 84% (95% CI 65.3%–93.6%) by intent-to-treat analysis and 91.3% (95% CI 73.2%–97.6%) by per-protocol analysis. One (4%) patient died, two (8%) discontinued due to intolerance and one (4%) experienced virological failure. The CD4/CD8 ratio and plasma lipids improved.

Conclusions: Dual therapy with etravirine plus raltegravir was well tolerated and maintained durable viral suppression in selected virologically suppressed patients for whom both PI and NRTI therapy was challenging.

Keywords: dual antiretroviral therapy, antiretroviral therapy efficacy, PI/NRTI sparing regimen

Introduction

Antiretroviral therapy has changed the natural history of HIV infection. However, antiretroviral therapy must be maintained for life. Its potential long-term adverse effects may interact synergistically with the ageing process, resulting in a higher incidence of comorbidities. The increasing number of non-antiretroviral drugs used to treat comorbidities may also place the patient at a higher risk of clinically meaningful interactions.[1,2] At a time when antiretroviral therapy was suboptimal, virological failure with cumulative resistance mutations was common. Surviving patients from the initial antiretroviral era may harbour resistance mutations despite having now achieved sustained virological suppression with currently available antiretroviral therapy. Nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors (PIs) have been substantially involved in the toxicity and resistance issues mentioned above, as they appeared earlier and have been more widely used than other classes of antiretrovirals, and older drugs within their classes were particularly toxic.[3,4]

New antiretrovirals, such as the integrase inhibitor raltegravir and the non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine, have not shown major limiting toxicities, are effective in patients with prior resistance to NRTIs and PIs and pose a low risk of clinically significant drug interactions.[5–10]

Nowadays, efficacy is less of a problem compared with previous times. A substantial number of HIV-infected patients from areas where antiretroviral therapy is widely available have achieved sustained suppression of plasma HIV replication.[7] In contrast, the contributions of antiretroviral therapy to the development and progression of comorbidities and to the risk of potentially severe

interactions have gained increasing importance as HIV-infected patients are getting older. More than half of HIV-infected patients aged ≥50 years have been reported to suffer from two or more concomitant comorbidities.[8] In some of these patients, maintenance of antiretroviral therapy with combinations including NRTIs or PIs may be challenging.

We report here the preliminary 48-week efficacy and safety results of a longitudinal pilot study with a dual regimen containing etravirine plus raltegravir in antiretroviral-experienced HIV-infected patients unable to maintain NRTI and PI regimens.

Methods

Study population

We conducted a longitudinal study at Hospital Clinic Barcelona (Spain) in which patients receiving an NRTI-containing or a PI-containing regimen or both had their regimen switched to a regimen consisting of 200 mg of etravirine/12 h plus 400 mg of raltegravir/12 h due to any intolerance, toxicity or risk of drug interactions for both NRTIs and PIs.

Plasma HIV RNA was required to have been <50 copies/mL in the previous 6 months. Patients with acute antiretroviral discontinuations were allowed to enter the study as long as their clinical condition stabilized shortly after drug discontinuation. Patients already taking raltegravir or etravirine in combination with other antiretrovirals were not excluded.

Patients with prior documented virological failure to etravirine- or raltegravir-containing regimens were excluded. Patients with prior virological failures to nevirapine- or efavirenz-containing regimens were excluded if they had no genotypic resistance testing performed or if their genotypic resistance tests showed NNRTI mutations conferring any degree of resistance to etravirine according to the Stanford Drug Resistance Database.[11] Patients unable to satisfactorily comply with the study regimen for any reason were also excluded.

Participants were visited at baseline, at 1 month and every 3–6 months thereafter. At baseline, HIV-related data were collected, including years since HIV infection diagnosis, potential HIV transmission route, prior AIDS-defining events, and history and duration of exposure to antiretroviral therapy and previous virological failure; results of prior genotypic resistance testing were collected when available. The reason for switching antiretroviral therapy was also recorded at baseline. The clinical evaluation at each follow-up visit included the reason for the antiretroviral therapy switch and the tolerability of the new regimen. CD4 and CD8 cell counts and measurements of plasma HIV-1 RNA, triglycerides and total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol were performed. LDL cholesterol was measured indirectly whenever triglycerides were <400 mg/dL; otherwise it was measured directly. The total cholesterol/HDL cholesterol ratio was calculated and Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations were used to estimate renal function. Raltegravir plasma concentrations were determined by HPLC with a fluorescence detector (Multifluorescence Detector 2475; Waters, MA, USA) at 6 months.[12] Patients were followed for at least 12 months, until discontinuation of study therapy or until loss to follow-up, whichever came first. The HIV cohort database and this specific study were approved by the local research ethics committee. Written informed consent was obtained from all eligible patients before entering the study.

Outcome

Virological failure was defined as the first of two consecutive measurements of plasma HIV RNA ≥50 copies/mL separated by at least 2 weeks at month 1 or later. In cases of virological failure, serum samples were tested for resistance, including reverse transcriptase, protease and integrase genotyping of virus using the ViroSeq HIV-1 genotyping system according to the manufacturer's instructions (Applied Biosystems, Foster City, CA, USA).

Secondary endpoints were changes in CD4 and CD8 cell counts, CD4/CD8 ratio and fasting plasma lipids, incidence of possible adverse events related to treatment and improvement of condition or symptom underlying antiretroviral therapy switch.

Statistical analysis

Intent-to-treat and per-protocol analyses were done. Virological failure, discontinuation of antiretroviral therapy or loss to follow-up were considered therapeutic failures in the intent-to-treat analysis. In the per-protocol analysis, discontinuation of antiretroviral therapy or loss to follow-up were censored. The sign rank test was used to test the hypothesis that changes in laboratory and immunological parameters were different from 0. All analyses were carried out using SPSS software for Windows Version 15.0 (SPSS, Chicago, IL, USA).

Results

Population characteristics

Twenty-five patients were included between February 2009 and February 2012 and completed at least 48 weeks of follow-up, with a median (IQR) follow-up of 102 (52–150) weeks. The study profile is shown in Figure 1. Patients had received a median (IQR) of 9 (6–11) different antiretroviral regimens for a median (IQR) of 16 (15–20) years. The median (IQR) CD4+ T cell count at baseline was 391 (235–728) cells/mm^3. Raltegravir plasma concentrations at 6 months were adequate in all patients (median 0.2, IQR 0.1–0.3 μg/mL).

Antiretroviral regimens discontinued at baseline included an NRTI in 6 (24%), a PI in 10 (40%) and a combination of both in 9 (36%) patients. One patient had an etravirine-containing regimen, six patients had a raltegravir-containing regimen and three patients had an etravirine+raltegravir-containing regimen prior to changing to dual therapy. Although 16 (64%) patients were nevirapine experienced and 15 (60%) efavirenz experienced, most were etravirine naive (21, 84%). Eleven (44%) patients had previously experienced treatment with raltegravir. The characteristics of the participants are shown in Table 1.

Lipid alterations and lipodystrophy were the most prevalent reasons for switching (seven patients, 28%). Gastrointestinal disorders, such as diarrhoea, nausea and abdominal pain, were also reported in isolation or in association with lipodystrophy or risk of drug interactions. Other reasons were renal toxicity and neuropsychiatric symptoms. An association of two or more reasons was observed in eight (32%) patients. Causes of switching to dual therapy are shown in Table 2. Causes varied widely according to the previous regimen. For instance, all but one of those who changed due to gastrointestinal intolerance were receiving PI-based therapies. In addition, drug interaction and lipid abnormalities were all reported for all patients on PI-based therapy. Renal toxicity was a cause for switching in patients receiving tenofovir. Neuropsychiatric symptoms were mostly reported in efavirenz-treated patients. Lipodystrophy was a frequent reason for changing therapy in patients on NRTIs.

Virological failure to a prior regimen had been diagnosed in 21 (84%) patients and 15 (60%) had at least one resistance genotype

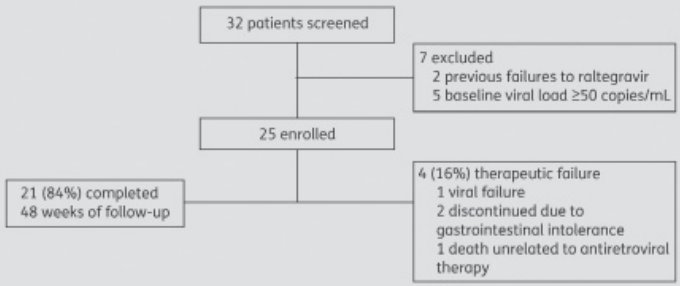

Figure 1. Study profile.

Table 1. Baseline demographic and HIV-related characteristics of patients ($n=25$) included in the study

Characteristic	Median (IQR) or *n* (%)
Age (years)	54 (49–62)
Male	13 (52)
Potential HIV transmission route	
heterosexual	6 (24)
men who have sex with men	11 (44)
injection drug users	6 (28)
blood transfusion	1 (4)
Years since HIV diagnosis	20 (16–22)
Prior AIDS-defining events	8 (32%)
Duration of exposure to antiretroviral therapy (years)	16 (15–20)
Number of previous antiretroviral regimens	9 (6–11)
Previous virological failure	21 (84)
Prior genotypic resistance testing	15 (60)
Current use of statins	2 (8)
CD4 cell count (cells/mm^3)	391 (235–728)
CD4 cell count (%)	21 (14–27)
CD8 cell count (cells/mm^3)	1077 (857–1347)
CD8 cell count (%)	53 (47–64)
CD4/CD8 ratio	0.42 (0.29–0.63)
Glucose (mg/dL)	98 (92–120)
Triglycerides (mg/dL)	198 (122–273)
Total cholesterol (mg/dL)	191 (160–244)
HDL cholesterol (mg/dL)	38 (33–50)
LDL cholesterol (mg/dL)	123 (97–145)
Total cholesterol/HDL cholesterol ratio	5.18 (4.23–5.55)
MDRD (mL/min/m^2)	92 (74–111)

test performed because of virological failure. By standard genotype testing, three or more NRTI mutations were observed in 9 (60%) patients and 11 (73%) presented more than four PI resistance mutations. Eight patients (32%) had a plasma sample containing NNRTI mutations; six individuals had an isolated 103N, one had 103N plus 98G and one patient had 190A isolated.

Table 2. Reasons for switching to dual therapy in the 25 patients included in the study

Reason	*n* (%)
Drug interaction only	3 (12)
Toxicity	
gastrointestinal symptoms	1 (4)
lipodystrophy	1 (48)
renal impairment	3 (12)
neuropsychiatric symptoms	3 (12)
Combination of causes	
gastrointestinal symptoms and drug interaction	1 (4)
gastrointestinal symptoms and lipodystrophy	7 (28)
lipid abnormalities and lipodystrophy	6 (24)

Virological and immunological response

At 48 weeks the therapeutic efficacy of dual therapy was 84% (21/25) (95% CI 65.3%–93.6%) by intent-to-treat analysis and 91.3% (21/23) (95% CI 73.2%–97.6%) by per-protocol analysis. Regarding the immunological response, at week 48 of follow-up there was a median increase of 114 cells/mm^3 in CD4+ T cell counts (IQR 217, −4; 21 patients, $P=0.075$) associated with a decrease of −232 cells/mm^3 in CD8+ T cell counts (IQR −6, −323; 23 patients; $P=0.020$) and an increase of 0.14 in the T4/T8 ratio (IQR 0.37, 0.06; 19 patients, $P=0.001$).

Virological failure was observed in one patient (4.0%, 95% CI 0.7%–19.5%) at week 28, with good compliance and an adequate raltegravir level (0.3 μg/mL). Resistance genotype testing revealed a high level of resistance to etravirine (103N, 179F, 179I, 181C and 225H) and no integrase mutations. The patient had been previously exposed to nevirapine and efavirenz with no documented virological failure and was receiving lamivudine, fosamprenavir/ritonavir and raltegravir before switching to etravirine/raltegravir dual therapy due to diarrhoea, dyslipidaemia, diabetes, lipodystrophy and osteoporosis. Diarrhoea as well as lipids improved with treatment. After confirmation of virological failure, therapy was changed to darunavir/ritonavir and maraviroc, achieving virological suppression. All 21 patients who reached week 48 continued on etravirine/raltegravir dual therapy, follow-up ranged from 51 to

194 weeks and no further treatment interruption or death was observed.

Safety and tolerability

Overall, two (8%) patients discontinued treatment due to gastrointestinal intolerance after 8 weeks, attributed to etravirine. There were no cases of rash. One patient died due to biliary sepsis at week 40; this was considered unrelated to antiretroviral therapy. Improvement of at least one of the conditions underlying therapy switch was found in 22 (88%) subjects. All three patients who changed due to abnormalities in renal function showed improvement in estimated glomerular filtration rate. All patients with gastrointestinal intolerance improved except for one case of diarrhoea in a patient with cirrhosis. Neuropsychiatric symptoms improved in all patients who discontinued efavirenz-based therapy.

Median percentage changes in chemistry tests from baseline to week 72 are shown in Figure 2. There was a decrease in median plasma triglyceride level of −27.78% (IQR −49.64%, 9.14%; $P=0.02$), glucose level of −7.06% (IQR −13.47%, 4.01%; $P=0.05$) and total cholesterol/HDL cholesterol ratio of −15.61 (IQR −24.87, 1.36; $P=0.001$) and an increase in HDL cholesterol of 6.96% (−7.17%, 34.31%, $P=0.02$) after 48 weeks of treatment. Some patients with a follow-up longer than 48 weeks (16 subjects) showed a further decrease in plasma triglycerides of −33.54% (IQR −58.63%, −6.65%; $P=0.05$) and total cholesterol/HDL cholesterol ratio of −26.32 (IQR −33.36, −5.31; $P=0.006$) 72 weeks after the

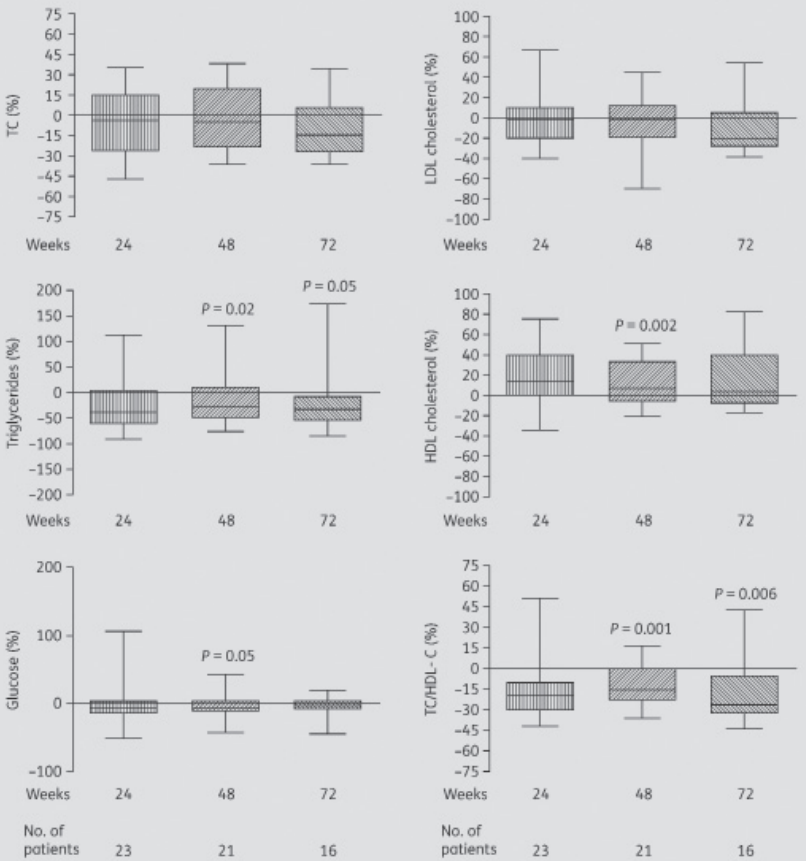

Figure 2. Median percentage changes in chemistry tests from baseline to week 72. TC, total cholesterol.

switch. There were no overall changes in estimated glomerular filtration rate, except in three patients who switched to dual therapy due to renal toxicity. No patient discontinued lipid-lowering drugs and two had the dosage reduced after changing to dual therapy. No patient interrupted treatment due to any laboratory-related adverse event.

Discussion

In the Hospital Clinic HIV Unit, where >4000 patients have been actively cared for in the previous 5 years, there were 25 patients over a 3 year period who had their regimen switched to etravirine plus raltegravir because of therapeutic concerns with both PIs and NRTIs. All patients were older than average in the HIV Unit and had a long history of HIV infection and extensive treatment experience, and changed to dual therapy mostly for tolerance and toxicity problems. The most frequent reasons for switching were metabolic issues and/or lipodystrophy, although many of them had two or more different reasons to enter the study. In this regard etravirine plus raltegravir may represent an interesting simple option considering that these drugs, so far, have not been associated with metabolic, CNS, renal or bone toxicities. Indeed, we observed a mild but significant reduction in triglycerides, total cholesterol/HDL cholesterol ratio and glucose levels.

Improvement in at least one of the conditions underlying regimen switch was reported in >80% of patients; these conditions were mostly gastrointestinal symptoms and lipid abnormalities but also included renal laboratory parameters. The improvement of the condition or symptom that motivated switching to dual therapy depended fundamentally on the frequency of the symptom/condition and its association with the antiretroviral regimen discontinued. In a recent study of the lipid-lowering effect of an etravirine-based regimen in 121 patients, lipids improved in >70% of patients, although a greater effect was observed, as expected, in those who switched due to lipid alterations, especially in fosamprenavir- and lopinavir-treatment patients.[13] In our study seven patients were using PI-based regimens when they changed to etravirine+raltegravir dual therapy (two darunavir, one lopinavir, one tipranavir, one fosamprenavir/ritonavir, one boosted atazanavir and one unboosted atazanavir). Despite hyperlipidaemia not being a common reason for a change in patients receiving darunavir and unboosted atazanavir, all patients presented lipid improvement and two had their dosage of lipid-lowering drugs reduced or discontinued. Consistent with this, in previous studies in which a PI was changed to raltegravir, fasting lipids improved irrespective of the PI that was discontinued.[9,10]

With respect to safety and tolerability, regardless of the report of two treatment discontinuations due to gastrointestinal intolerance, probably related to etravirine, clinical tolerability was good; there were no cases of rash or any laboratory-related adverse events.

Although caution is needed with cross-study comparisons, the efficacy results seen in this study are similar to reported data obtained in similar settings. In a recent published database review reporting 18 patients who were switched from different antiretroviral regimens to 200 mg of etravirine twice daily plus 400 mg of raltegravir twice daily, 94.4% achieved virological suppression to <50 copies/mL at 6 months and 83.3% at 12 months (intent-to-treat analysis).[14]

It is important to note that in the present study virological failure was restricted to one patient (4%), whose resistance genotype testing confirmed a high level of resistance to etravirine with no integrase mutations. The patient had several comorbidities and long-term NRTI and PI adverse effects. Initially, he maintained virological control and showed improvement in metabolic parameters, but at week 28 experienced virus rebound (viral load 103 400 copies/mm^3) in spite of having raltegravir plasma concentrations in the therapeutic range.

A single mutation is often enough to cause resistance to the first-generation NNRTIs nevirapine and efavirenz, but the development of resistance to etravirine is a complex phenomenon that requires the coexistence of multiple mutations, and varies with the number and type of mutations present.[15] In the present study, standard genotypic resistance testing after virological failure revealed the presence of the five NNRTI resistance mutations K103N, V179F, V179I, Y181C and P225H. The presence of K103N is often associated with efavirenz failure and confers cross-resistance to nevirapine, but in isolation has no effect on susceptibility to etravirine.[6,16] It was present in seven patients at baseline. V179F and Y181C are 2 of the 13 etravirine DUET study mutations.[17,18] By itself, V179F has no effect on etravirine susceptibility, but in combination with Y181C it causes high-level etravirine resistance. V179F almost always occurs in combination with Y181C and they are often selected by etravirine.[15,19] The K103N and Y181C mutations frequently emerge in patients failing on first-generation NNRTIs, with K103N tending to emerge more in patients failing efavirenz and Y181C in patients failing nevirapine.[20] In the case with virological failure, the patient had been treated with efavirenz and nevirapine, for 6 years in total, with no documented virological failure.

The risk of interactions between antiretrovirals is an important issue in the management of HIV-infected patients. The potential of etravirine for reducing raltegravir concentrations and the need to adjust the dosage of raltegravir in HIV-infected patients who are also receiving etravirine is an issue of concern. However, several studies, besides ours, have confirmed the therapeutic viability of this combination.[21–24] We found therapeutic drug levels to be adequate in all patients including the case of viral failure, who developed high-level of etravirine resistance but no raltegravir mutations.

Beyond virological suppression, patients experienced a decrease in CD8 count and an increase in CD4/CD8 ratio, which suggests that virological suppression with this study regimen was as effective as expected, given the prior regimens. Recently, the CD4/CD8 ratio has been independently associated with T cell activation,[25,26] and immune activation has been associated with premature ageing and adverse outcomes, and is therefore an important issue to be considered in long-term HIV treatment.[1]

The present study has some potential limitations. First, we should be cautious in interpreting data from studies on a limited number of patients, aside from the inherent limitations of the observational design. Second, genotype resistance tests were not available for all patients. Third, standard direct PCR sequencing detects the most common circulating HIV-1 variants within a clinical sample but may overlook less-prevalent drug-resistant variants.[27]

Despite these limitations, this study provides novel and clinically relevant data on the simplification of antiretroviral therapy in selected patients in whom there are concerns about both PI and NRTI therapy. These data reinforce the conception of an individual-

based approach taking into account cumulative resistance mutations and historical treatment as a strategy to optimize treatment outcome in pre-treated patients when switching to a better tolerated antiretroviral regimen. Based upon these considerations, our results suggest that a regimen with etravirine and raltegravir might ensure convenience and tolerance and provide enough potency to achieve viral suppression in selected pre-treated patients. The relatively low genetic barrier to resistance of raltegravir, together with the cross-resistance within the NNRTI class and the possibility of accumulating mutations, does not encourage its use in individuals who experienced viral replication during raltegravir treatment and/or who have accumulated NNRTI resistance mutations. Taking all these considerations together, we believe that this strategy deserves further attention in an adequately powered, randomized clinical trial.

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Author contributions

P. M. participated in study design, data acquisition and data analysis, and drafted the manuscript. E. M. and J. M. G. conceived the study and participated in study design and data analysis, and drafted the manuscript. M. L., M. M.-R., A. G.-C., M. L., J. M. and J. L. B. participated in recruiting patients, data acquisition, supervising data integrity and analysis, and critically revised the manuscript. I. P. performed the statistical analysis. All authors were involved in data interpretation and read and approved the final manuscript.

References

1 Deeks SG, Phillips AN. HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. *BMJ* 2009; **338**: a3172.

2 Marzolini C, Elzi L, Gibbons S *et al.* Prevalence of comedications and effect of potential drug-drug interactions in the Swiss HIV Cohort Study. *Antivir Ther* 2010; **15**: 413–23.

3 Worm SW, Sabin C, Weber R *et al.* Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis* 2010; **201**: 318–30.

4 Ryom L, Mocroft A, Kirk O *et al.* Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. *J Infect Dis* 2013; **207**: 1359–69.

5 Steigbigel RT, Cooper DA, Kumar PN *et al.* Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med* 2008; **359**: 339–54.

6 Katlama C, Clotet B, Mills A *et al.* Efficacy and safety of etravirine at week 96 in treatment-experienced HIV type-1-infected patients in the DUET-1 and DUET-2 trials. *Antivir Ther* 2010; **15**: 1045–52.

7 Costagliola D, Ledergerber B, Torti C *et al.* Trends in virological and clinical outcomes in individuals with HIV-1 infection and virological failure of drugs from three antiretroviral drug classes: a cohort study. *Lancet Infect Dis* 2012; **12**: 119–27.

8 Guaraldi G, Orlando G, Zona S *et al.* Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* 2011; **53**: 1120–6.

9 Eron JJ, Young B, Cooper DA *et al.* Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. *Lancet* 2010; **375**: 396–407.

10 Martínez E, Larrousse M, Llibre JM *et al.* Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS* 2010; **24**: 1697–707.

11 Liu TF, Shafer RW. Web resources for HIV type 1 genotypic-resistance test interpretation. *Clin Infect Dis* 2006; **42**: 1608–18.

12 Poirier JM, Robidou P, Jaillon P. Quantification of the HIV-integrase inhibitor raltegravir (MK-0518) in human plasma by high-performance liquid chromatography with fluorescence detection. *J Chromatogr B Analyt Technol Biomed Life Sci* 2008; **867**: 277–81.

13 Casado JL, de Los Santos I, Del Palacio M *et al.* Lipid-lowering effect and efficacy after switching to etravirine in HIV-infected patients with intolerance to suppressive HAART. *HIV Clin Trials* 2013; **14**: 1–9.

14 Calin R, Paris L, Simon A *et al.* Dual raltegravir/etravirine combination in virologically suppressed HIV-1-infected patients on antiretroviral therapy. *Antivir Ther* 2012; **17**: 1601–4.

15 Vingerhoets J, Tambuyzer L, Azijn H *et al.* Resistance profile of etravirine: combined analysis of baseline genotypic and phenotypic data from the randomized, controlled Phase III clinical studies. *AIDS* 2010; **24**: 503–14.

16 Vingerhoets J, Azijn H, Fransen E *et al.* TMC125 displays a high genetic barrier to the development of resistance: evidence from in vitro selection experiments. *J Virol* 2005; **79**: 12773–82.

17 Madruga JV, Cahn P, Grinsztejn B *et al.* Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2007; **370**: 29–38.

18 Lazzarin A, Campbell T, Clotet B *et al.* Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. *Lancet* 2007; **370**: 39–48.

19 Tambuyzer L, Vingerhoets J, Azijn H *et al.* Characterization of genotypic and phenotypic changes in HIV-1-infected patients with virologic failure on an etravirine-containing regimen in the DUET-1 and DUET-2 clinical studies. *AIDS Res Hum Retroviruses* 2010; **26**: 1197–205.

20 Bannister WP, Ruiz L, Cozzi-Lepri A *et al.* Comparison of genotypic resistance profiles and virological response between patients starting nevirapine and efavirenz in EuroSIDA. *AIDS* 2008; **22**: 367–76.

21 Anderson MS, Kakuda TN, Hanley W *et al.* Minimal pharmacokinetic interaction between the human immunodeficiency virus nonnucleoside reverse transcriptase inhibitor etravirine and the integrase inhibitor raltegravir in healthy subjects. *Antimicrob Agents Chemother* 2008; **52**: 4228–32.

22 Ménard A, Solas C, Mokthari S *et al*. Etravirine-raltegravir, a marked interaction in HIV-1-infected patients: about four cases. *AIDS* 2009; **23**: 869–71.

23 Do VT, Higginson RT, Fulco PP. Raltegravir dosage adjustment in HIV-infected patients receiving etravirine. *Am J Health Syst Pharm* 2011; **68**: 2049–54.

24 Sandkovsky U, Swindells S, Moore R *et al*. Acceptable plasma concentrations of raltegravir and etravirine when administered by gastrostomy tube in a patient with advanced multidrug-resistant human immunodeficiency virus infection. *Pharmacotherapy* 2012; **32**: 142–7.

25 Sainz T, Serrano-Villar S, Díaz L *et al*. The CD4/CD8 ratio as a marker T-cell activation, senescence and activation/exhaustion in treated HIV-infected children and young adults. *AIDS* 2013; **27**: 1513–6.

26 Serrano-Villar S, Gutiérrez C, Vallejo A *et al*. The CD4/CD8 ratio in HIV-infected subjects is independently associated with T-cell activation despite long-term viral suppression. *J Infect* 2013; **61**: 57–66.

27 Varghese V, Shahriar R, Rhee SY *et al*. Minority variants associated with transmitted and acquired HIV-1 nonnucleoside reverse transcriptase inhibitor resistance: implications for the use of second-generation nonnucleoside reverse transcriptase inhibitors. *J Acquir Immune Defic Syndr* 2009; **52**: 309–15.

ARTICLE 6

Creatine kinase elevation in HIV-1-infected patients receiving raltegravir-containing antiretroviral therapy: a cohort study.

Polyana Monteiro, Iñaki Perez, Judit Pich, Jose Maria Gatell and Esteban Martínez.

Hospital Clínic—IDIBAPS, University of Barcelona, Barcelona.

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Creatine kinase elevation in HIV-1-infected patients receiving raltegravir-containing antiretroviral therapy: a cohort study

Polyana Monteiro*, Iñaki Perez, Judit Pich, Jose Maria Gatell and Esteban Martínez

Hospital Clinic—IDIBAPS, University of Barcelona, 08036 Barcelona, Spain

*Corresponding author. Tel: +34-93-227-55-74; Fax: +34-93-451-44-38; E-mail: polymonteiro@hotmail.com

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Objectives: To evaluate the incidence and risk factors for significant creatine kinase elevation in HIV-1-infected patients who were prescribed a raltegravir-containing antiretroviral therapy.

Design: A retrospective analysis of a prospectively collected cohort involving all consecutive patients who were prescribed a raltegravir-containing antiretroviral regimen between June 2005 and December 2010.

Methods: Significant creatine kinase elevation was defined as an elevation of at least 3-fold from the upper limit of normal (ULN) (grade 2, WHO classification) while receiving raltegravir. Blood analysis at each visit included at least creatine kinase, as well as plasma HIV-1 RNA and CD4 cell count.

Results: There were 475 patients who had been exposed to raltegravir for a median of 11.5 (IQR 8.2–15.2) months. An increase of creatine kinase ≥3-fold ULN was detected in 53 (11.2%) patients, representing an incidence of 3.8/100 person-years. Symptoms were reported by seven patients (1.5%), they showed either grade 1 ($n=3$) or 2 ($n=4$) creatine kinase increases. The median duration of raltegravir therapy before creatine kinase elevation was 5.9 (IQR 3.3–9.3) months. Evidence of creatine kinase elevation prior to raltegravir therapy [hazard ratio (HR) 3.30; 95% CI 1.59±6.86; $P=0.001$], abnormal baseline creatine kinase (HR 3.24; 95% CI 1.63±6.45; $P=0.001$) and male gender (HR 4.17; 95% CI 1.33±1.27; $P=0.001$) were identified as independent risk factors for creatine kinase elevation during raltegravir treatment.

Conclusions: Although ~1 in 10 patients on raltegravir therapy developed significant creatine kinase elevation as defined in this study, symptoms were uncommon, not severe and occurred in patients with easily identifiable risk factors.

Keywords: HIV, creatine kinase elevation, raltegravir, antiretroviral therapy, adverse effects

Introduction

Musculoskeletal manifestations are well-recognized complications of HIV itself (polymyositis) and also of treatment with some antiretroviral agents, such as zidovudine. Nowadays manifestations of AIDS are uncommon and zidovudine is no longer preferentially recommended, with polymyositis and zidovudine-induced creatine kinase (CK) elevations being now rarely reported.[1]

The first drug of a new class of antiretrovirals that targets the integrase enzyme, raltegravir, has been involved in cases of myotoxicity. It was approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) in 2007. At that time, among the reported laboratory abnormalities were transient elevations in serum CK that did not require drug interruption.[2] During the post-marketing surveillance, at least four cases of rhabdomyolysis have been published.[3–6]

Currently, raltegravir is indicated in combination with other drugs for treatment-naive and treatment-experienced patients in cases of virological or immunological failures, or in simplification of treatment.[7–9] It has the advantage of being generally well tolerated and having few drug–drug interactions.[10–12] Although a causal relationship with raltegravir has not been clearly established, the FDA, the EMA and the manufacturer recommend using raltegravir with caution in individuals at increased risk of myopathies [Isentress (raltegravir) package insert; Merck & Co., Inc., Whitehouse Station, New Jersey, 2007].

Grade 3/4 CK elevations have been reported in clinical trials, but there may be lower-grade CK elevations, whose incidence, clinical repercussions and risk factors are currently unclear.[13] To gain further insight into the potential for raltegravir-associated CK elevation in clinical practice, we evaluated the incidence and risk factors for CK elevation in HIV-1-infected

patients who were prescribed a raltegravir-containing antiretroviral therapy (ART).

Methods

Study population

We conducted a retrospective analysis of the HIV cohort at Hospital Clinic Barcelona (Spain). This cohort has been previously described.[14–16] All HIV-1-infected adults who initiated a raltegravir-containing antiretroviral regimen from June 2005 to December 2010 in the setting of routine clinical practice were eligible for the study. Data on clinical and analytical variables were prospectively collected in a database. Other risk factors for CK elevation, including evidence of CK elevation prior to raltegravir therapy or rhabdomyolysis, alcohol or illicit drug consumption, or use of any therapeutic drug potentially related with myotoxicity such as zidovudine and statins, were all assessed by review of medical records, as this information is actively collected in the clinical database. Blood analysis at each visit included CK, plasma HIV-1 RNA, CD4 cell count, as well as other chemistry and cell analyses.

Patients were followed from the initiation of the raltegravir-containing regimen until the censoring date (31 May 2011). Other censoring reasons were death, lost to follow-up and withdrawal of raltegravir for any reason. The HIV cohort database as well as this retrospective study were approved by the local research Ethics Committee.

Outcome

Considering that raltegravir Phase III studies (protocols 018 and 019) used high thresholds of CK to define abnormalities (greater than six times the upper limit of normal [ULN]), we set lower limits in order to increase the sensitivity and avoid individuals with milder abnormalities being excluded.[17,18] For this purpose we relied on the WHO recommendations for the classification of acute and subacute toxic effects. CK elevations were graduated as grade 1 or mild (2.0–2.9×ULN), grades 2 and 3 or moderate (3.0–4.9×ULN and 5–9.9×ULN, respectively) and grade 4 or clinically significant (≥10×ULN). Significant CK elevation was defined whenever there was an increase of at least 3-fold in CK from the ULN during raltegravir therapy. Nevertheless, CK elevation less than three times the ULN were further considered in order to characterize the incidence and the clinical impact of low-grade abnormalities. CK elevations of any grade in at least one consecutive visit were also analysed to characterize the incidence of persistent abnormalities. CK elevation was defined as symptomatic when it was accompanied by the presence of any unexplained muscular complaint (muscle pain, muscle tenderness, proximal muscle weakness, or muscle cramps) during raltegravir treatment.

Statistical analysis

Variables are expressed as mean and standard deviation, median and IQR, or proportions, as appropriate. CK elevation incidence analysis was performed considering the date of starting raltegravir and the incidence curve was estimated using the Kaplan–Meier product-limit method. The potential baseline factors associated with CK elevation were assessed using the generalized log-rank test (univariate Cox model analysis). Factors associated with a P value <0.10 in the univariate analysis were considered as candidate factors for the multivariate analysis (baseline CK, prior history of CK elevation, male gender). We used forward stepwise and backward elimination subset selection methods to identify variables that predicted survival. The hazard ratio (HR) and the associated 95% CI for each predictor were calculated. Statistical significance was defined as a bilateral P value <0.05. All statistical analyses were carried out using SPSS (release 15).

Results

Population characteristics

In this study 475 patients (75% males) had a raltegravir-containing ART initiated, with a mean (±SD) age of 46 (±9) years. Two subjects with missing information were excluded. Four-hundred-and-thirty-five (91.6%) patients had already received ART for a median period of 116 months (IQR 54.5–170.3 months) before starting raltegravir. The median duration of raltegravir-containing regimens was 11.5 months (IQR 8.1–15.2 months). The median CD4 cell count was 374 cells/mm^3 (IQR 234–570 cells/mm^3) and the median HIV RNA was 1.87 $\log_{10}$ copies/mL (IQR 1.69–4.07 $\log_{10}$ copies/mL). Blood analyses were scheduled as part of routine clinical care every 3–6 months.

Grade 1 CK elevations were seen in 48 patients (10.1%), and grade 2 or 3 CK elevations were seen in 45 patients (9.5%). Figure 1 shows the study population according to CK grade elevations. CK elevations as defined in this study developed in 53 patients (11.2%), representing an incidence of 3.8/100 person-years. The characteristics of participants are shown in Table 1. The median duration of therapy before CK elevations became apparent was 5.9 months (IQR 3.3–9.3 months). Of all cases of any CK elevations 123 (25.9%) persisted in at least one consecutive visit. Grade 4 toxicity was observed in only five patients (1.0%), and there were no cases of rhabdomyolysis. There was no need to discontinue raltegravir due to CK elevations in any patient. Kaplan–Meier estimates of the incidence of a 3-fold increase in CK are shown in Figure 2.

Symptoms were reported by seven patients—1.5% of the cohort representing 13% of patients with CK elevations. In these patients the CK increase was grade 1 in three and grade 2 in the remaining four. Clinical symptoms developed a median period of 7.8 months after starting raltegravir (IQR 6.5–22.5 months). The symptoms reported were muscle pain and/or contractures. None of the patients was taking statins concomitantly; one patient reported use of alcohol and two were on regimens with zidovudine, even though it had been prescribed for more than 1 year. None of these symptomatic patients had previously experienced similar symptoms or had muscular enzymes increased with ART prior to raltegravir initiation.

Risk factors for CK elevation

After adjustment in the multivariate model, abnormal baseline CK (CK ≥2×ULN when starting raltegravir; HR 3.24; 95% CI 1.63–6.45; P=0.001), evidence of CK elevation prior to raltegravir therapy (HR 3.30; 95% CI 1.59–6.86; P=0.001) and male gender (HR 4.17; 95% CI 1.33–1.27; P=0.001) were associated with a higher risk of CK elevation.

Discussion

The frequency of CK elevations in clinical trials varies according to the definition of abnormality and the characteristics of the patients included in the study. In the Phase II trial protocol 005, with multiresistant virus-infected patients, the incidence of CK >10×ULN was similar between raltegravir and placebo (6% versus 4%).[19] On the other hand, in the BENCHMRK Phase III trial, also with treatment-experienced patients, CK

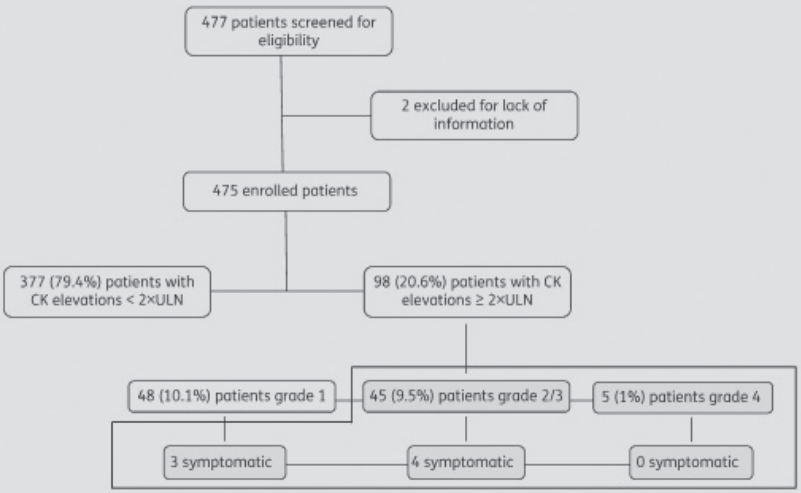

Figure 1. Study population according to CK grade elevations. Grade 1 (2.0–2.9×ULN), grades 2 and 3 (3.0–4.9×ULN and 5–9.9×ULN, respectively), and grade 4 (≥10×ULN). Patients with CK elevations according to the study definition (53 subjects) are highlighted in grey and boxed.

Table 1. Baseline characteristics of patients starting raltegravir-containing regimens included in the study[a]

	Significant CK elevation			
	yes	no	Total	P^b
Participants (*n*)	53 (11.2%)	422 (88.8%)	475 (100.0%)	—
Male (*n*)	47 (88.7%)	307 (72.7%)	356 (74.6%)	0.01
ARV naive (*n*)	5 (9.4%)	35 (8.3%)	40 (8.4%)	0.78
Drug/alcohol use (*n*)	5 (9.4%)	26 (6.2%)	31 (6.5%)	0.36
Use of zidovudine (*n*)	3 (5.7%)	12 (2.8%)	15 (3.1%)	0.27
Use of statins (*n*)	14 (26.4%)	69 (16.4%)	83 (17.6%)	0.14
CK elevation prior to RAL therapy (*n*)	10 (18.9%)	20 (4.7%)	30 (6.3%)	<0.01
CK (mg/dL)	154 (100–268)	99 (64–145)	104 (67–154)	<0.01
CD4 T cells (cells/mm^3)	381 (260–551)	369 (233–575)	374 (234–570)	0.95
HIV-1 RNA (log_{10} copies/mL)	2.00 (1.69–4.04)	1.8 (1.69–4.09)	1.85 (1.69–4.07)	0.48

ART, antiretroviral; therapy; CK, creatine kinase; RAL, raltegravir.
[a]Variables are expressed as mean and standard deviation, median and interquartile range, or proportions, as appropriate.
[b]Comparison between significant and non-significant CK elevation.

≥20×ULN was more common in the raltegravir group than in the placebo group (3% versus 0.8%).[18] In the 96 week protocol 004, with treatment-naive patients, 6.3% in the raltegravir arm experienced CK ≥10×ULN versus 2.6% of patients in the efavirenz arm.[20] Other prospective studies have described a frequency of grade 3/4 CK elevations between 5% and 13%, and most of the cases had no clinical repercussions.[21–25]

The frequency of significant CK elevation with raltegravir-containing regimens as defined in this study was 11.2%, with an incidence of 3.8/100 person-years. This incidence is higher than that observed in Phase II and III trials, a finding already expected since we used lower limits for detecting laboratory abnormalities. A recent study by the Italian SCOLTA cohort analysed CK elevation in patients receiving raltegravir- or darunavir-based therapy. They reported CK elevations >200 U/L in 8.9% of patients treated with raltegravir, thus including what we consider grade 1 CK elevation; adding this to the incidence observed for grade 2–4 in this study the incidence is also higher (20.6%).[26]

Among those who met the definition of CK elevations in our study, 64.2% had grade 2 CK elevations (3.0–4.9×ULN) and

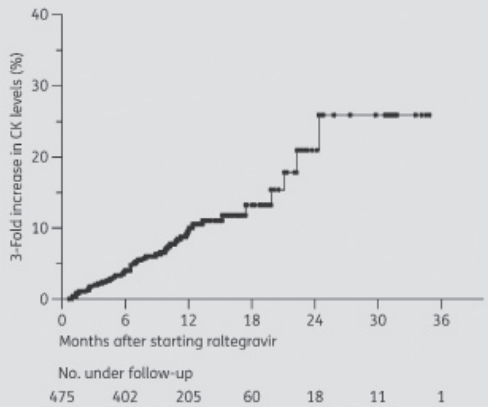

Figure 2. Kaplan–Meier time to 3-fold increase in CK levels from starting raltegravir.

30.2% grade 3/4 CK elevations (>5.0×ULN) with no clinical repercussions at all. The cases of symptomatic CK elevations were very few and the intensity of symptoms was not related to CK increase. Moreover, there were other possible underlying factors (alcohol consumption and zidovudine use) that may have played a part in symptomatic patients. Madeddu *et al.* also found no relation between CK increase and muscle pain or weakness.[26]

We did not find any reports of rhabdomyolysis and only a minority (1.0%) of patients presented with a CK ≥10×ULN. The Phase III STARTMRK trial reported only one case of severe CK elevation who recovered without discontinuing therapy.[27] Since raltegravir was approved by the FDA in 2007, four cases of rhabdomyolysis have been reported to be associated with raltegravir-containing regimens. Causation could not be established in any of them since all the patients also had potential risk factors for CK elevations in addition of raltegravir: renal chronic dysfunction plus use of foscarnet, use of pravastatin and previous CK abnormality.[3–6]

Since raltegravir and statins share glucuronidation as a common metabolic pathway, there is a potential risk for drug–drug interaction.[28] In this study, 17.3% of patients were receiving raltegravir concomitantly with statins, but this fact was not identified as an independent risk factor in multivariate analysis. In accordance with this, a cross-over study in 24 healthy subjects determined the effect of raltegravir on pravastatin pharmacokinetics, and vice versa; although participants were followed for a very short time, there were no CK elevations or any other types of myopathy.[29]

Because it occurs so rarely, especially clinically significant CK elevations, little is known about the pathogenic mechanisms of raltegravir-associated CK elevation. In this study, evidence of CK elevation prior to raltegravir therapy and baseline CK ≥2×ULN were independent risk factors for CK elevation during raltegravir treatment. This finding raises the suspicion of a possible individual predisposition involved in the pathogenesis of muscular toxicity associated with raltegravir.

A potential limitation of our study is the lack of a control group. However, data from clinical trials have shown that the incidence of CK elevations was higher in patients receiving raltegravir-containing regimens. We also have to acknowledge that the physical activity of the patients was not routinely recorded in their clinical charts, so we cannot exclude a potential effect of strenuous physical exercise on muscular enzymes. What we aimed to do in our study was to analyse the impact and clinical repercussions of a CK increase in a cohort of patients receiving raltegravir-based ART in the setting of routine clinical practice. Although the risk of developing rhabdomyolysis in persons treated with raltegravir-containing antiretroviral regimens must be considered in prescribing therapy for HIV-1-infected patients, our data suggest that the risk of CK elevation in patients initiating raltegravir-containing regimens is low and not severe. As shown in this study, routine laboratory monitoring of CK might be of little value since the majority of subjects had mild CK elevations with no clinical complaints.

In summary, an increase of at least 3-fold in CK in a cohort of patients starting raltegravir-containing ART was not unusual, but clinical symptoms were uncommon and not severe. Evidence of CK elevation prior to raltegravir therapy and abnormal baseline CK might be helpful to identify those patients at higher risk. The results of this study do not support a monitoring approach different from that considered for other ART regimens to prevent severe adverse muscular reactions.

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Author contributions

P. M. participated in the study design, in the acquisition of data and drafted the manuscript. I. P. performed the statistical analysis. E. M. conceived the study and its design, drafted the manuscript and revised the manuscript. P. M., I. P., J. P., J. M. G. and E. M. were involved in the interpretation of data. All authors read and approved the final manuscript.

References

1 Nguyen BY, Reveille JD. Rheumatic manifestations associated with HIV in the highly active antiretroviral therapy era. *Curr Opin Rheumatol* 2009; **21**: 404–10.

2 Connelly SM. Raltegravir NDA 22-145. *U.S. Food and Drug Administration Division of Antiviral Products Antiviral Drugs Advisory Committee Medical Review*. Washington, DC: FDA, 2007: 45–111.

3 Zembower TR, Gerzenshtein L, Coleman K *et al*. Severe rhabdomyolysis associated with raltegravir use. *AIDS* 2008; **22**: 1382–4.

4 Dori L, Buonomini AR, Viscione M *et al*. A case of rhabdomyolysis associated with raltegravir use. *AIDS* 2010; **24**: 473–5.

5 Masiá M, Enriquez R, Sirvent A *et al*. Severe acute renal failure associated with rhabdomyolysis during treatment with raltegravir. A call for caution. *J Infect* 2010; **61**: 189–90.

6 Croce F, Vitello P, Dalla Pria A *et al*. Severe raltegravir-associated rhabdomyolysis: a case report and review of the literature. *Int J STD AIDS* 2010; **21**: 783–5.

7 Department of Health and Human Services. *Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. http://www.aidsinfo.nih.gov/ContentFiles/vguidelines/AdultandAdolescentGL.pdf (27 June 2012, date last accessed).

8 European AIDS Clinical Society (EACS). *Guidelines for clinical management and treatment of HIV-infected adults in Europe. Version 6.0 (October 2011)*. http://www.europeanaidsclinicalsociety.org/images/stories/EACS-Pdf/EACSguidelines-v6.0-English.pdf (27 June 2012, date last accessed).

9 Martinez E, Larrousse M, Llibre JM *et al*. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. *AIDS* 2010; **24**: 1697–707.

10 Hicks C, Gulick RM. Raltegravir: the first HIV type 1 integrase inhibitor. *Clin Infect Dis* 2009; **48**: 931–9.

11 Okeke NL, Hicks C. Role of raltegravir in the management of HIV-1 infection. *HIV AIDS* 2011; **3**: 81–92.

12 Rockstroh JK, Lennox JL, Dejesus E *et al*. Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naive human immunodeficiency virus-1-infected patients: 156-week results from STARTMRK. *Clin Infect Dis* 2011; **53**: 807–16.

13 Lee FJ, Carr A. Tolerability of integrase inhibitors. *Curr Opin HIV AIDS* 2012; **7**: 422–8.

14 Garcia F, de Lazzari E, Plana M *et al*. Long-term CD4+ T-cell response to highly active antiretroviral therapy according to baseline CD4+ T-cell count. *J Acquir Immune Defic Syndr* 2004; **36**: 702–13.

15 Gratacós L, Tuset M, Codina C *et al*. Antiretroviral therapy of HIV infection: duration and reasons for changing the first therapeutic regimen in 518 patients. *Med Clin* 2006; **126**: 241–5.

16 Martínez E, Milinkovic A, Buira E *et al*. Incidence and causes of death in HIV-infected persons receiving highly active antiretroviral therapy compared with estimates for the general population of similar age and from the same geographical area. *HIV Med* 2007; **8**: 251–8.

17 Steigbigel RT, Cooper DA, Kumar PN *et al*. Raltegravir with optimized background therapy for resistant HIV-1 infection. *N Engl J Med* 2008; **359**: 339–54.

18 Steigbigel RT, Cooper DA, Teppler H *et al*. Long-term efficacy and safety of raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials. *Clin Infect Dis* 2010; **50**: 605–12.

19 Gatell JM, Katlama C, Grinzstejn B *et al*. Long term efficacy and safety of the HIV integrase inhibitor raltegravir in patients with limited treatment options in a phase II study. *J Acquir Immune Defic Syndr* 2010; **53**: 456–63.

20 Markowitz M, Nguyen BY, Gotuzzo E *et al*. Sustained antiretroviral effect of raltegravir after 96 weeks of combination therapy in treatment-naive patients with HIV-1 infection. *J Acquir Immune Defic Syndr* 2009; **52**: 350–6.

21 Eron JJ Jr, Rockstroh JK, Reynes J *et al*. Raltegravir once daily or twice daily in previously untreated patients with HIV-1: a randomized, active-controlled, phase 3 non-inferiority trial. *Lancet Infect Dis* 2011; **11**: 907–15.

22 Reynes J, Lawal A, Pulido F *et al*. Examination of noninferiority, safety, and tolerability of lopinavir/ritonavir and raltegravir compared with lopinavir/ritonavir and tenofovir/emtricitabine in antiretroviral-naïve subjects: the progress study, 48-week results. *HIV Clin Trials* 2011; **12**: 255–67.

23 Young B, Vanig T, Dejesus E *et al*. A pilot study of abacavir/lamivudine and raltegravir in antiretroviral-naïve HIV-1-infected patients: 48-week results of the SHIELD trial. *HIV Clin Trials* 2010; **11**: 260–9.

24 Yazdanpanah Y, Fagard C, Descamps D *et al*. High rate of virologic suppression with raltegravir plus etravirine and darunavir/ritonavir among treatment-experienced patients infected with multidrug-resistant HIV: results of the ANRS 139 TRIO trial. *Clin Infect Dis* 2009; **49**: 1441–9.

25 Gallien S, Braun J, Delaugerre C *et al*. Efficacy and safety of raltegravir in treatment-experienced HIV-1-infected patients switching from enfuvirtide-based regimens: 48 week results of the randomized EASIER ANRS 138 trial. *J Antimicrob Chemother* 2011; **66**: 2099–106.

26 Madeddu G, Soddu V, Ricci E *et al*. Muscle symptoms and creatine phosphokinase elevations in patients receiving raltegravir in clinical practice: results from a multicenter study. In: *Abstracts of the Tenth International Congress on Drug Therapy in HIV Infection, Glasgow, UK, 2010*. Abstract P111, p. 71. International AIDS Society, Geneva, Switzerland.

27 Lennox JL, Dejesus E, Berger DS *et al*. Raltegravir versus efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. *J Acquir Immune Defic Syndr* 2010; **55**: 39–48.

28 Ramkumar K, Neamati N. Raltegravir: the evidence of its therapeutic value in HIV-1 infection. *Core Evid* 2010; **4**: 131–47.

29 van Luin M, Colbers A, van Ewijk-Beneken Kolmer EW *et al*. Drug–drug interactions between raltegravir and pravastatin in healthy volunteers. *J Acquir Immune Defic Syndr* 2010; **55**: 82–6.

“A vida não se resolve com palavras”.

João Cabral de Melo Neto

Discussion

SUMMARY OF MAIN FINDINGS

Article 1: Effectiveness of ritonavir-boosted protease inhibitor monotherapy in the clinical setting: same results as in clinical trials? The PIMOCS Study Group

Article 2: Changes in cardiovascular biomarkers in HIV-infected patients switching from ritonavir-boosted protease inhibitors to raltegravir

Article 3: Abacavir/lamivudine versus tenofovir/emtricitabine in virologically suppressed patients switching from ritonavir-boosted protease inhibitors to raltegravir

Article 4: Rosuvastatin versus protease inhibitor switching for hypercholesterolaemia: a randomised trial

Article 5: Dual therapy with etravirine plus raltegravir for virologically suppressed HIV-infected patients: a pilot study

Article 6: Creatine kinase elevation in HIV-1-infected patients receiving raltegravir-containing antiretroviral therapy: a cohort study

The literature brings evidence that a variety of factors have contributed to the multiple benefits of ARV; however the most important probably is tolerability profile and lack of long-term toxicity, leading to a high grade of adherence to the treatment and consequently high rates of virological control. Durable control of virus replication restores immunologic function, reduces HIV-associated morbidity and prolongs life. Furthermore, effective ART suppress plasma VL and is highly effective at preventing HIV transmission.

Now that ART may be considered for all HIV-1-infected patients, and life expectancy is greatly prolonged by suppressive therapy, many of the complications due to long-term toxicity of HIV treatment and age-associated comorbidities may become more prominent. In this regard it is important to evaluate the impact of new interventions to prevent or reduce the morbidity associated with HIV-1 infection and its treatment.

This thesis addresses the efficacy and safety of different approaches to limit potential complications of ART, with the purpose of improving ARV tolerability in HIV-infected adults.

PI/rs are still widely used, even though they have more adverse effects than other agents. We describe its effectiveness and safety when use in monotherapy in routine care settings. It is well known that RAL is very potent, easy to take and has a good safety profile. We discuss its impact on cardiovascular biomarkers after switching from PI/r-based therapy, as well its efficacy and safety when used in combination with ABC/3TC backbone.

Regarding CVD, we report the results of the Statin or Switch (SoS) trial for the treatment of hypercholesterolaemia. Simplification of regimens to dual therapy avoiding NRTI and PI, were also explored in a pilot study of efficacy and safety of dual therapy with ETR plus RAL. Finally, we address the implication of RAL in muscular toxicity.

SUMMARY OF MAIN FINDINGS

Article 1: Effectiveness of ritonavir-boosted protease inhibitor monotherapy in the clinical setting: same results as in clinical trials? The PIMOCS Study Group.

Between January 2004 and July 2012, 664 patients started LPV/r or DRV/r monotherapy (65% DRV/r) for maintenance of viral suppression in routine care setting. Most patients (90%) had been previously exposed to a PI and one-third of them had experienced virological failure (VF) on a PI-containing regimen. The median time with undetectable VL prior to PIMT initiation was 49 months.

After a median follow-up of 16 months, 78% of patients remained free from therapeutic failure (TF) by modified intention-to-treat analysis (stopping or changing PIMT due to any reason equals failure, except for changes from one PIMT to another PIMT, censoring data at treatment change). By ITT analysis (VF, stop or change for any reason equals failure), cumulative survival at 12 months was 83% for DRV/r and 77% for LPV7r (P=0.001 between PIs). This effectiveness is higher than that reported from a observational study from the French cohort [168] and matched the results of randomized clinical trials. [172, 173, 198]

The use of PI monotherapy for maintenance of viral suppression has been evaluated in several trials with different endpoints to evaluate its efficacy. Four trials evaluated DRV/r monotherapy (n=785: MONET, MONOI, MONARCH, PROTEA), five evaluated LPV/r monotherapy (n=592: OK-04, KalMo, KALESOLO, KRETA, MOST) and one evaluated both DRV/r and LPV/r (MRC PIVOT, n=587). [199] Small differences in the PIMT outcome between clinical trials and our cohort are probably driven by patients characteristics. Indeed, the risk of VF in our study, 12% after 16 months of PIMT, was similar to that observed in randomized clinical trials. [172, 173, 175, 201]

The probability of being free from VF after 12 months was 91% in general, 92.7% for DRV/r and 88.4% for LPV/r (P=0.139 between PIs). At month 24 of follow-up, time to TF was significantly shorter with LPV/r, but no differences were seen between groups considering time to VF. When comparing the effectiveness of LPV/r versus DRV/r, the TF rate was higher among patients receiving LPV/r. However, these differences must be taken cautiously as baseline characteristics were not comparable and no differences in terms of viral response were seen between PIs. Adverse events leading to PIMT discontinuation were relatively rare. Twenty patients switched from one PIMT to another, the overall majority from LPV/r to DRV/r due to gastrointestinal or lipid disturbances. Stopping PIMT in LPV/r group was twice more frequent than in DRV/r group (36 % x 17%).

Consistent with data obtained in randomized clinical trials, almost one-quarter of patients receiving PIMT in our study had transient viremia, with no differences in the incidence risk between both PI/r combinations. [173, 202, 203] Low-level replication and transient elevations of VL are frequently observed during PIMT, underscoring a lower antiviral potency of PIMT and less forgiveness for suboptimal adherence as compared with ART. [172, 173]

A total of 158 patients stopped PIMT, mostly for VF but also for adverse events and other reasons. The strongest predictor of VF in our cohort was time on a suppressive viral regimen before PIMT switching. The risk of VF was almost 2-fold higher among patients with viral suppression < 24 months previous to change and 1.6-fold higher in patients with a CD4+ cell count nadir < 200 cells/mm3. In agreement, short duration of viral suppression and low CD4+ cell count nadir have been reported as risk factors for virologic failure in previous studies. [168, 169, 171, 175]

Remarkably, one-third of patients in our study had previously failed on a PI-containing regimen, but the risk of VF was not increased in these patients, which highlights the high genetic barrier of both LPV/r and DRV/r. We found few patients experiencing VF to have emergent PI resistance mutations, a finding consistent with previous trials. [205, 206] Indeed, in the PIVOT trial patients exposed to monotherapy did not have a higher risk of losing therapeutic options. [170]

The results of recent studies provide an interesting intermediate approach between 3 active drugs and PIMT . The GARDEL study, demonstrated noninferior results from LPV/r plus 3TC vs. LPV/r plus 2 NRTIs as initial therapy, at 48 weeks of follow up. There were more grade 2/3 adverse events in the triple arm and only 2 patients developed M184V after virologic failure in both arms. [207] The OLE study provided further information with this combination in virologically suppressed patients. Switching suppressed patients to LPV/r plus 3TC or FTC was noninferior to the triple-agent regimen. [208] But not all 2-drug strategies with a PI/r are successful. The HARNESS trial was stopped earlier for higher rates of virologic failure in patients who switched to ATV/r plus RAL compared with ATV/r plus 2 NRTIs, with 2 cases of integrase inhibitor resistance. [209]

Indeed, In 2014 International Antiviral Society-USA guidelines included alternative PI regimens for first-line in specific situations, such as a patient at high risk of CVD or osteoporosis or one with chronic kidney disease who is HLA-B*5701–positive. These alternative regimens include combination of DRV/r plus RAL, LPV/r plus 3TC, and DRV/r plus RAL in selected circumstances. [32]

One important concern regarding PIMT is whether patients who achieve viral suppression in blood also achieve suppression in the central nervous system. Data on this issue are limited and somewhat conflicting. [171, 210, 211, 212] In our cohort, two patients had evidence of CNS replication. Both cases had low CD4+ cell count nadir (<100 cells/mm3). To date, risk factors for CNS replication among patients on PIMT is far from clear, but incidence seems to be low. [170, 198, 199]

In conclusion, the safety and efficacy of a maintenance strategy with PIMT in a routine care setting matched the results of randomized clinical trials, almost 80% of patients receiving PIMT in our cohort remained free from TF after a median of 16 months of therapy and 88% remained free from VF. Long duration of sustained viral suppression (>2 years) prior to PIMT initiation and high CD4+ cell count nadir (>200 cells/mm3) were independently associated with a favourable outcome.

Article 2: Changes in cardiovascular biomarkers in HIV-infected patients switching from PI/r to RAL.

The SPIRAL study was a 48-week, multicenter, open-label, randomized trial in which HIV-1-infected adults virologically suppressed for at least 6 months on PI/r-based therapy were randomized (1:1) to switch from the PI/r to RAL or to continue on PI/r-based therapy. Two hundred and thirty-three patients (RAL, n=119; PI/r, n=114) remained on their allocated therapy for 48 weeks. None of them had experienced virological failure throughout the study follow-up. Most common PIs at entry were LPV/r (45%) and ATV/r (36%). Eigthy-five (36%) patients had experienced prior virological failure, but the median of virological suppression was 71 months before randomization.

Although there were no differences in any lipid parameter at baseline, TG, TC, LDL-c, and HDL-c significantly decreased in RAL group relative to PI/r group. In patients switching to RAL, TG decreased significantly more when the PI discontinued was LPV/r than when it was ATV/r. Similarly, TC decreased significantly more when the PI discontinued was LPV/r.

Switching from PI/r to RAL in the SPIRAL trial led not only to significant changes in plasma lipids but also to significant changes in several cardiovascular biomarkers associated with inflammation, insulin resistance, and hypercoagulability, although not in those associated with endothelial dysfunction. There were significant decreases in hsCRP, MCP-1, osteoprotegerin, IL-6, TNF-a, insulin and D-dimer in the RAL group relative to the PI/r group, whereas IL-10, ICAM-1, VCAM-1, E-selectin, P-selectin, and adiponectin remained

unchanged. There were few and not strong significant correlations between changes in lipids and changes in biomarkers. TG, TC and LDL-c changes at 48 weeks were weakly correlated with hsCRP, MCP-1, and insulin. These results suggest that switching from PI/r to RAL induced changes in inflammation, insulin resistance, and hypercoagulability biomarkers that were not completely explained by lipid changes.

Changes in biomarkers and lipids in patients switching from PI/r to RAL could be theoretically due to discontinuation of protease inhibitors, introduction of RAL, or both. A recent randomized study also reported significant decreases in hsCRP, IL-6, and D-dimer at 24 and 48 weeks in virologically suppressed patients switching from ENF to RAL. [213] Another study measured markers of immune activation, microbial translocation, and T-cell exhaustion in 15 treatment naive patients initiating RAL-containing therapy and compared results with historical controls who had received a similar duration of non-RAL therapy and to HIV-uninfected controls. At 48 weeks, levels of immune activation, microbial translocation, and T-cell exhaustion were reduced from baseline to levels that were significantly lower than those in the historical controls but higher than those in uninfected patients. [214]

The ACTG 5262 trial evaluated biomarkers of immune activation, microbial translocation and inflammation during initial ART with a NRTI-sparing regimen consisting of DRV/r plus RAL. After 48 weeks, assays were completed for 107 participants. DRV/r plus RAL led to a decline in soluble CD14, interleukin-6 and interferon-γ-inducible protein-10 levels. T cell activation remained higher in subjects with virological failure, driven for high baseline VL. [215] In a randomized trial in HIV-infected women with central adiposity, a switch to RAL was associated with statistically significant declines in sCD14 compared with subjects remaining on a PI or NNRTI-based therapy. [216]

In contrast, a recent prospective study of ART-naive subjects described changes in immune activation and inflammation markers after initiation of TDF/FTC with RAL, ATV/r or DRV/r . Interestingly, RAL did not have a greater impact on decreasing systemic inflammation and immune activation markers compared to PIs. Furthermore, some markers remained elevated despite successful ART therapy, suggesting incomplete reversal of inflammation and immune activation despite effective treatment. [217]

The results of the SPIRAL study suggest that PI/r-containing therapy may be not only associated with increased plasma lipids but also with increased markers of inflammation, insulin resistance, and hypercoagulability relative to RAL-containing therapy. These findings are in accordance with previous studies showing associations between protease in-

hibitors and elevated fibrinogen [63] levels in patients and increased TNF-a and IL-6 expression in macrophages cultures. [218]

Nevertheless, changes in biomarkers study were marginally related to changes in lipids, suggesting that PI/r-related effects on cardiovascular biomarkers are not driven only by lipid changes. In contrast to other biomarkers, we did not detect changes in markers of endothelial dysfunction. Although first-generation PI were able to induce endothelial dysfunction through different pathways, [65] contemporary PI such as LPV/r or ATV have not been shown to induce endothelial dysfunction in healthy volunteers [219] or HIV-1-infected patients [122].

Finally, different markers were investigated, but there are other potentially important ones that were not assessed in this study. This study and others suggest that there may be differential effects of ART on cardiovascular biomarkers associated with inflammation, insulin resistance and hypercoagulability, but it remains to be seen whether these findings are clinically relevant.

Recently, case- control studies have reported associations between plasma markers of inflammation, coagulation and gut barrier dysfunction, and the risk of non AIDS-defining events and mortality. [220, 221] The ALLRT cohort, evaluated the impact of markers of inflammation (IL-6), monocyte activation/microbial translocation (sCD14), coagulation (D-dimer), and T-cell activation/dysfunction before the initiation and during ART. Elevated levels of IL-6, sCD14, D-dimer and soluble tumor necrosis factor receptors (sTNFR1 and sTNFR2), were associated with the occurrence of non AIDS-related morbidities and death, independently of traditional risk factors, other comorbid conditions, age, treatment regimen, and treatment-mediated changes in CD4+ T-cell counts. [222] However, further studies are needed to determine whether ART-mediated changes in any inflammatory biomarker are associated with reduced morbidity and mortality.

Article 3: Abacavir/lamivudine versus tenofovir/emtricitabine in virologically suppressed patients switching from PI/r to RAL.

NRTI combinations form the backbone of the majority of first-line regimens for treatment of HIV-1 infection. Data with ABC/3TC plus new drugs, such as RAL, are more limited compared to TDF/FTC, and are restricted to ARV naive patients. The efficacy and safety of ABC/3TC was compared to TDF/FTC when each was combined with either RAL or PI/r in the SPIRAL trial. The analysis included 197 patients (72.16%), 143 (73%) treated with

TDF/FTC and 54 (27%) with ABC/3TC. In the population assigned to RAL, patients taking ABC/3TC were older and a higher proportion had suffered previous virological failure than those taking TDF/FTC.

With regard to efficacy there were no real differences between the regimens. Rates of treatment failures (11%) and virological failures (4%) were similar in both groups. In the STARTMRK study TDF/FTC plus RAL demonstrated no inferiority when compared with EFV. [70, 71, 67] The SHIELD trial was a prospective, observational study enrolling 35 ARV-naive patients who initiated ABC/3TC plus RAL. At week 48 regimens was considered effective and well-tolerated. [224]

In terms of lipids, the data suggest that the improvement in plasma lipids expected when PIs are replaced by RAL in virologically suppressed HIV-1-infected patients should not be worse when the combination of NRTIs used is ABC/3TC than when it is TDF/FTC. Switching individuals from PI to RAL resulted in greater improvements in lipid profiles in patients on ABC/3TC than in patients on TDF/FTC, suggesting that the combination of an ABC and PI might have distinct synergistic lipid effect. This finding was unexpected and the reason is not clear. These results should be taken with caution because of the small sample size and the lack of significance at 48 weeks in most lipid changes.

The overall incidence of adverse effects was also similar between groups (61% ABC/3TC x 57% TDF/FTC). Although no patient discontinued ABC/3TC due to adverse events, four (2.80%) patients (all in the PI/r group) discontinued TDF/FTC because of kidney or bone events. There were no discontinuations of any combination of NRTIs due to adverse events when combined with RAL.

Because ABC/3TC and TDF/FTC may have a different impact on comorbidities, choosing between them could be helpful to customize an optimal therapy. Nephrotoxicity is the most important adverse event associated with TDF treatment. [42] In addition, the ACTG 5224 (metabolic substudy of ACTG 5202) demonstrated significantly greater losses in bone mineral density in both the lumbar spine and hip in TDF/FTC-treated participants compared with ABC/3TC. [221] Moreover, treatment with ABC may lead to a potentially life-threatening event. Hypersensitivity reactions occurs in 5% of patients treated with ABC although risk may be minimized by prior testing for the presence of HLA-B*5701 allele which is strongly linked to ABC hypersensitivity reactions. [38, 40] ABC has also been linked in to increased risk of myocardial infarction and so far evidence of this association remains inconsistent. [41, 42, 178, 179]

Prior comparisons between both fixed-dose NRTI combinations in virologically suppressed HIV-infected adults have also shown similar results in the BICOMBO and STEAL trials. Although in the BICOMBO trial there were more discontinuations with ABC/3TC due to hypersensitivity because patients had not been previously tested for HLA-B*5701. [181, 103] In summary, this analysis of the SPIRAL trial does not suggest that outcomes of ABC/3TC are worse than those of TDF/FTC when combined with RAL in virologically suppressed HIV-1-infected adults.

Article 4: Rosuvastatin versus protease inhibitor switching for hypercholesterolaemia: a randomised trial.

The Statin or Switch (SoS) trial randomized 43 HIV-1-infected adults with fasting hypercholesterolaemia and increased cardiovascular risk to start rosuvastatin (23 patients) or to switch PI/r (20 patients). The majority of patients were using LPV/r (51%) at enrolment followed by ATV/r (28%), and DRV/r (11%). Within the PI/r switch group, RAL (45%) and RPV (20%) were the most common PI/r substitutions.

At week 12, rosuvastatin was more effective at lowering TC than PI/r switching regardless of the baseline TC level. Rosuvastatin use was associated with an 11.6% greater decline in fasting TC at week 12 than PI/r . The fall in TC was also larger when the baseline TC was higher. Reductions in total and LDL-c in the rosuvastatin group were comparable to those observed with rosuvastatin therapy in other HIV-1-infected cohorts. [196, 228] Likewise, compared to earlier PI/r switch studies. [148, 149, 156, 161] TC, LDL- c and TG reductions achieved within our PI/r switch group were similar. It should be noted, however, that none of these previous clinical trials included participants with clinically elevated cardiovascular risk; thus the lipid-lowering strategies to results to date are of uncertain clinical significance.

Our results concur with those of the only prior study to compare a statin (pravastatin) with PI/r switching. [197] However, this earlier study used EFV as a switch option, despite its known lipid effects, [229] and also used pravastatin, a less potent statin [196]. In fact, as progressively fewer patients are commenced on non-preferred PI/r such as LPV/r as initial ART, PI/r switching as a hypolipidemic strategy is likely to become less clinically relevant. This would leave statin therapy as the intervention of choice for hypercholesterolaemia for the majority of adults receiving a PI/r.

Mean absolute cardiovascular risk reduction was higher with rosuvastatin than PI/r switching, but the observed lipid changes in this study were insufficient to affect a significant between-group difference for either the Framingham or D:A:D scores. The mean scores nevertheless fell from baseline with either intervention.

Rosuvastatin is affected by PI/r interactions that inhibit its metabolism, increasing mean exposure by 1.5, 2, and 3-fold with concomitant twice-daily DRV/r, twice-daily LPV/r, and once-daily ATV/r, respectively. [230] Despite pharmacokinetic boosting, rosuvastatin-related laboratory adverse events were absent. There were no instances of myalgia or myopathy, grade 3 or 4 laboratory adverse events, or premature discontinuation, and quality-of-life assessments were similar between the groups. Nevertheless, most participants (65%) experienced at least one clinical adverse event. More drug-related events were observed in the PI/r switch group (10 events vs. 1 event, p=0.001); mainly gastrointestinal symptoms. One participant assigned to rosuvastatin experienced loss of virological suppression; adjudged to be secondary to suboptimal ART adherence.

The significantly greater estimated insulin secretion with rosuvastatin at week 12 was an unexpected finding. Rosuvastatin has been associated with a higher incidence of diabetes mellitus compared to placebo in the JUPITER study over a median two-year period of treatment. [231] The mechanism is unknown, and the few studies examining the effect of rosuvastatin on insulin resistance parameters have given inconsistent results. [232, 233] Both interventions showed minimal, but favourable changes in both the D-dimer and LDL particle size; a larger sample size may reveal greater changes and significant between-group differences.

In this randomized study for treatment of hypercholesterolaemia in adults with increased cardiovascular risk, both rosuvastatin and PI/r switching yielded decreases in total and LDL-c, by week 4 that were maintained through to week 12. Rosuvastatin 10 mg/day led to deeper decreases in total and LDL-c, both parameters that either determine CV risk or are targets for intervention, with fewer adverse events. Subgroup analyses revealed rosuvastatin was more effective than PI/r switching at all levels of hypercholesterolaemia , and in participants receiving regimens based on preferred PI/r.

Article 5: Dual therapy with etravirine plus RAL for virologically suppressed HIV-infected patients: a pilot study.

For a long time, many different combinations have been studied to identify a suitable regimen that excludes NRTIs with safety, tolerability, and equally effective as the standard NRTI-containing regimens. Recent studies have shown promising results with combinations of a PI/r plus INSTI in treatment-naive patients. [234, 235, 236] The overall results showed that that dual therapy was noninferior than standard triple therapy but raised questions on the noninferiority of those regimens in the subset of patients with CD4+ counts < 200 cells/mm3 and HIV-1 RNA > 100,000 copies/mL. Anyhow, PI/r remain an important component of those NRTI-sparing regimens; the searching for a regimen that excludes both NRTI and PI class is clearly an area for extensive debate.

In the HIV Unit of Hospital Clinic of Barcelona, where 4000 patients have been actively cared for in the previous 5 years, twenty-five patients over a 3 year period had their regimen switched to ETR plus RAL because of tolerance and toxicity problems with both PIs and NRTIs. The most frequent reasons for switching were metabolic issues and/or lipodystrophy and gastrointestinal symptoms. Other reasons were renal toxicity and neuropsychiatric symptoms, although many of them had two or more different reasons to enter the study. Improvement in at least one of the conditions underlying regimen switch was reported in 80% of patients; these conditions were mostly gastrointestinal symptoms and lipid abnormalities but also included renal laboratory parameters.

All patients were older than average in the HIV Unit, had a long history of HIV infection and extensive treatment experience. The majority of patients (76%) were in PI-based regimens before changing to dual therapy and although were EFV or NVP-experienced more than 80% was ETR naive and 44% had previously experienced treatment with RAL.

Virological failure to a prior regimen was diagnosed in 21 (84%) patients, 73% presented more than four PI resistance mutations, and 32% had a plasma sample containing NNRTI mutations. At 48 weeks the therapeutic efficacy of dual therapy was 84% by ITT analysis and 91.3% by per-protocol analysis. All 21 patients who reached week 48 continued on ETR/RAL dual therapy, follow-up ranged from 51 to 194 weeks and no further treatment

interruption or death was observed. Regarding the immunological response, at week 48 of follow-up there was a median increase of 114 cells/mm3 in CD4+ T cell counts and of 0.14 in the T4/T8 ratio.

The efficacy results seen in this study are similar to reported data obtained in similar settings with the same combination. Calin et al analyzed 18 patients who were switched from different ARV regimens to 200 mg of ETR twice daily plus 400 mg of RAL twice daily, in ITT analysis 94.4% achieved virological suppression at 6 months and 83.3% at 12 months and only one patient who started treatment with detectable VL presented virological failure. [164] Recently, Casado et al evaluated prospectively 25 virologically suppressed and largely pre-treated patients, who were switched to ETR plus RAL. There were no cases of virological failure and only one participant changed therapy due to a rash. [237]

RAL-based regimens might suppose a risk of resistance at virologic failure, even more in a context of a dual therapy that exclude PI, in this study virological failure was observed in one patient at week 28, with good compliance and an adequate RAL level (0.3 mg/mL). Resistance genotype testing revealed a high level of resistance to ETR (103N, 179F, 179I, 181C and 225H) and no integrase mutations. This finding suggest that RAL might have a higher genetic barrier than we have supposed so far. Consistent with this thought, recent data from the ACTG 5257, a very large open-label phase III trial in which more than 1800 treatment-naive participants were randomized to either ATV/r, RAL or DRV/r plus FTC-TDF backbone, showed that at week 96, only 11 from 600 patients (2%) randomized to RAL developed an integrase inhibitor resistance mutation. [80]

Not surprisingly, lipid levels improved in all patients receiving RAL, even in those who were on DRV/r and unboosted ATV prior to switch, and two individuals had their dosage of lipid-lowering drugs reduced or discontinued. Consistent with this, in previous studies in which a PI was changed to RAL, fasting lipids improved irrespective of the PI that was discontinued. [148, 149] With respect to safety and tolerability, regardless of the report of two treatment discontinuations due to gastrointestinal intolerance, clinical tolerability was good; there were no cases of rash or any laboratory-related adverse events.

Given that, the results suggest that a regimen with ETR and RAL might ensure convenience and tolerance and provide enough potency to achieve viral suppression in selected pre-treated patients. There is a need for powered randomized trials to rigorously evaluate this strategy in order to optimize long-term patient outcomes.

Some very novel combinations of INSTI and NNRTI are been studied as maintenance therapy with some interesting and promising results in treatment-naive patients. An investigational HIV-1 INSTI and dolutegravir analogue was given in association with RPV to patients with suppressed viremia after an induction regimen of the same INSTI plus TDF/FTC. The virologic efficacy results at week 48 were remarkable, with more than 90% of patients experiencing successful virologic suppression. This may be the first large study with a 2 drug maintenance regimen that does not include a PI/r. [238]

Article 6: Creatine kinase elevation in HIV-1-infected patients receiving RAL-containing ART: a cohort study.

INSTIs represent a relatively new class with several agents that have proven to be efficacious and well tolerated and, depending on which is chosen, may provide options for virtually all patients. Currently there are 3 drugs from this class among the recommended options for first-line therapy, and two of them (EVG and dolutegravir) are now available as a STR. RAL was the first representative of this drug class and therefore has the longest post marketing experience in comparison to other INSTIs. It was first recommended for use in treatment-experienced patients with multidrug-resistance HIV [71] and now is considered an excellent first-line option for treatment-naive patients, as a switch option for PI-based regimens in suppressed patients and as alternative regimen in the context of NRTI-sparing regimens.

Most safety data regarding muscle adverse events in RAL-containing regimens are available from clinical trials and the results vary according to the definition of abnormality and to the characteristics of the patients included. We evaluated the incidence and risk factors for CK elevation in 475 HIV-1-infected patients who were prescribed a RAL-containing regimen in the setting of routine clinical practice. Significant CK elevation was defined an increase of at least 3-fold in CK from the ULN during RAL therapy. The frequency of significant CK elevation with RAL-containing regimens was 11.2%, with an incidence of 3.8/100 person-years. This incidence was higher than that observed in phase II and III trials, a finding already expected since we used lower limits for detecting laboratory abnormalities.

Since RAL was approved by the FDA in 2007, few cases of rhabdomyolysis have been reported to be associated with RAL-containing regimens. In these cases, other identifiable risk factors for rhabdomyolysis were present in different associations, except in the most recent case report. A 32-year-old, Asian male who lacked risk factors associated with rhabdomyolysis, developed rhabdomyolysis with a rapid onset in only 4 days after

switching from LPV/r to RAL 400 mg twice daily plus ddI and lamivudine. [86] We did not find any reports of rhabdomyolysis and only a minority (1.0%) of patients presented with a CK ≥10×ULN.

Clinical symptoms, muscle pain and/or contractures, developed a median period of 7.8 months after starting RAL (IQR 6.5–22.5 months). Symptomatic CK elevations were very few (7/98, 7.1%) and the intensity of symptoms was not related to CK increase, in agreement with the other two observational studies published to date. [239, 240] Moreover, there were other possible underlying factors (alcohol consumption and ZDV use) that may have played a part in symptomatic patients. Male sex was associated with significant CK elevation, as also observed in others observational studies. [240, 241] A possible explanation for this finding could be that male patients are more likely to undergo strenuous physical exercise during sports or job activities compared with females. Lee et al found strenuous exercise to be independently associated with muscle toxicity. [239]

The REALMRK was a multi-centre, open-label, single-arm observational study, conducted to assess efficacy and safety of RAL in patients with different categories of treatment experience and in groups often underrepresented in clinical trials, women and patients from diverse racial and ethnic backgrounds. In a population of 206 patients (47% female, 74% black and 10% naive) from 34 sites, increased creatine kinase (grade 2 or higher) was more common in men (10%) than women (0%) but occurred with similar frequency in blacks (5%) and nonblack (6%). One patient had a serious event of rhabdomyolysis, which was considered related to RAL, although the patient's urine toxicology was positive for cocaine, which can cause rhabdomyolysis. [241]

A cross-sectional, 2-arm prevalence study compared the prevalence of skeletal muscle toxicity in HIV-infected adults receiving RAL to a control group. Skeletal muscle toxicity was defined by the presence of one of the following components: (1) isolated CK elevation, (2) myalgia; (3) proximal myopathy on examination (4) rhabdomyolysis. In the study 318 participants (159 RAL, 159 controls) were evaluated by a mean of 28 months of RAL exposure. Skeletal muscle toxicity was present in 37% of the RAL versus 19% of the control group ($p<0.001$). There were significant differences in myalgia (19 vs. 3%, $p<0.001$) and proximal myopathy (4 vs. 0%, $p=0.030$). However, no significant difference was found in the proportion of CK increases and myalgia and myopathy were seen in patients with normal or only low level elevations in plasma CK. [239]

We find, elevation prior to RAL therapy and abnormal baseline CK to be independent risk factors for CK elevation during RAL treatment, what might suggest a possible individual

predisposition to muscular toxicity. These findings were consistent to a recent retrospective analysis by Calza et al. In 155 patients receiving a RAL-containing regimen 21% of patients presented isolated CK elevation, with an incidence of 4.2/100 person-years. Among factors significantly associated with CK elevation were previous use of zidovudine, higher baseline CK levels, previous increase of the CK levels, and a higher body mass index. As in other observational studies, frequency of myalgia and muscle weakness was low (<3%).[242]

A recent multicentre phase II trial assessed the safety and efficacy of two doses of raltegravir in combination with TDF/FTC in HIV patients co-infected with tuberculosis. 155 patients taking rifampicin as part of a standard tuberculosis treatment were randomly allocate to receive either EFV, RAL 400 mg or RAL 800mg twice a day. Although authors did not present in detail data of CK or muscle symptoms the number of serious adverse events in general were similar in all three groups. [243]

Thus, although myopathy seems to be a rare event, 1 in 10 patients on RAL therapy developed signification creatine kinase elevation, symptoms were uncommon and not severe. As observed by Lee et al [239], CK used alone may not be a sensitive marker of muscle toxicity in the setting of longstanding RAL therapy and patients receiving RAL should be actively monitored for myalgia and myopathy.

CONTRIBUTIONS AND FUTURE PERSPECTIVES

Our findings suggest that the potential benefit of RAL lays beyond virological control, with improvement in lipids and inflammatory markers, but it remains to be seen whether differential effects of ARV therapies on cardiovascular biomarkers are clinically relevant. Prospective cohort studies of long-term outcomes of ART that incorporate the biomarkers identified in this and other studies might address this question.

RAL have shown to be effective and well tolerate in virologically suppressed HIV-infected adults when used in combination with ABC/3TC, a combination less studied than TDF/FTC. In accordance, recently was approved the single-tablet coformulation of ABC, 3TC and the integrase inhibitor dolutegravir, an important step forward for treatment of HIV-1. The study on dual therapy provided novel and clinically relevant data on the simplification of ART in selected patients in whom there are concerns about both PI and NRTI therapy. This approach needs to be validated in prospective studies. From the perspective of muscle toxicity our findings confirm that RAL is safe in routine clinical setting, although 1 in 10 patients on RAL developed significant creatine kinase elevation, as defined in the study.

Collectively, these data support and concord with the current experts' recommendation of RAL as one of the preferred backbones of first-line ART. Another point to consider is the possibility of transmitted integrase resistance becomes a problem in the future. Nevertheless, new data suggest that concern is not yet upon us. [244] Similarly, as more inhibitors of integrase with higher genetic barrier are becoming available, switching to drugs other than RAL may become a valuable strategy to be investigated. Hopefully, RAL will also become affordable and available for patients in many resource-limited countries in the near future.

PI monotherapy may have an important role in long-term management of HIV infection, yet with a lower antiviral potency as compared with standard triple therapy and carrying concerns regarding ongoing viral replication in the CNS. Whereas maintaining viral suppression, it minimizes long-term toxicity related to NRTI; maintain an armamentarium for future treatment options, and save costs what makes this strategy very appealing in the setting of economic restrictions.

Modification of suppressive regimens is an important issue that, until recently, received little attention in international guidelines. European guidelines accept PIMT with DRV/r or LPV/r as a valid option for persons with intolerance to NRTIs, for treatment simplification or even for illicit drug users with documented frequent interruption of ART. In all circumstances, this strategy only applies to persons without history of failure on prior PI-based therapy and who have had HIV-VL < 50 copies/mL in at least the past 6 months and who do not have chronic hepatitis B. [33, 34]

In our study higher CD4+ cell count nadir was associated with a favourable PIMT outcome. In this regard, measurement of the size of HIV reservoirs could help to identify individuals who could benefit from this exceptional treatment, and deserve further research.

However, for some patients maintenance of a triple therapy based on PI is mandatory. In this situation treatment of comorbidities might be the most appropriate option. Combination of a PI-based therapy with a lipid lowering drug, in this particular case, rosuvastatin, have demonstrated to be safe and effective in reducing TC. Furthermore, for some situations a dual intervention (PI/r switch plus statin) may be needed to better achieve LDL-c targets. This intervention may be more potent that each one separately and could be of interest for future investigation.

While an HIV vaccine is in progress, efforts are needed to fully exploit all the potential of ART in maintaining viral suppression. Indeed, viral suppression will not only decrease HIV-1-associated morbidity and reduce transmission rates but may also decrease immune activation, a factor known to contribute to metabolic disorder. As knowledge on noninfectious complications continues to grow along with ongoing improvement on ART, we will be able to develop newer strategies to limit their impact on those living with HIV-1 and to assure they may age with optimal health.


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CONCLUSIONS

1. Effectiveness of ritonavir-boosted protease inhibitor monotherapy in clinical practice is consistent with data from clinical trials. Sustained viral suppression prior to initiation of monotherapy and nadir CD4 cell count are associated with a favourable outcome.

2. Switching from ritonavir-boosted protease inhibitors to raltegravir leads to significant changes in cardiovascular biomarkers associated with inflammation, insulin resistance, and hypercoagulability.

3. Abacavir/lamivudine exhibits similar efficacy and tolerability as tenofovit/emtricitabine in virologically suppressed patients switching from ritonavir-boosted protease inhibitors to raltegravir.

4. In adults with hypercholesterolaemia and increased cardiovascular risk, rosuvastatin 10 mg/day for 12 weeks produced larger decreases in total cholesterol and low-density lipoprotein cholesterol than ritonavir-boosted protease inhibitors switching.

5. Dual therapy with etravirine plus raltegravir is well tolerated and maintained durable viral suppression in selected virologically suppressed patients for whom both protease inhibitors and nucleoside reverse transcriptase inhibitor therapy is challenging.

6. Significant creatinine kinase elevation is observed in approximately one out of ten patients during treatment with raltegravir. Evidence of creatinine kinase elevation prior to raltegravir therapy and higher creatinine kinase at baseline are independent risk factors for creatinine kinase elevation during treatment with raltegravir.

REFERENCES

1. Gap report. Geneva, Joint United Nations Programme on HIV/AIDS, 2014. Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Gap_report_en.pdf. Date last accessed: 4 April 2015.
2. Martínez E, Milinkovic A, Buira E, De Lazzari E, León A, Larrousse M, et al. Incidence and causes of death in HIV-infected persons receiving highly active antiretroviral therapy compared with estimates for the general population of similar age and from the same geographical area. HIV Med. 2007;**8**:251–8.
3. Marin B, Thiébaut R, Bucher HC, Rondeau V, Costagliola D, Dorrucci M, et al. Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. AIDS. 2009;**23**(13):1743–53.
4. Hasse B, Ledergerber B, Furrer H, Battegay M, Hirschel B, Cavassini M, et al. Morbidity and aging in HIV-infected persons: The swiss HIV cohort study. Clin Infect Dis. 2011;**53**:1130–9.
5. Lewden C, Chene G, Morlat P, Raffi F, Dupon M, Dellamonica P, et al. HIV-infected adults with a CD4 cell count greater than 500 cells/mm3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. J Acquir Immune Defic Syndr. 2007;**46**(1):72–7.
6. Zwahlen M, Harris R, May M, Hogg R, Costagliola D, de Wolf F, et al. Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries. Int J Epidemiol. 2009;**38**(6):1624–33.
7. Cockerham L, Scherzer R, Zolopa A, Rimland D, Lewis CE, Bacchetti P, et al. Association of HIV infection, demographic and cardiovascular risk factors with all-cause mortality in the recent HAART era. J Acquir Immune Defic Syndr. 2010;**53**(1):102–6.
8. Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis. 2011;**53**(11):1120–6.
9. Peters B, Post F, Wierzbicki A, Phillips A, Power L, Das S, et al. Screening for chronic comorbid diseases in people with HIV: The need for a strategic approach. HIV Med. 2013;14(Suppl 1):1–11.
10. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med. 2011;**62**:141–55.
11. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med. 2008;**5**(10):e203.
12. Triant VA, Meigs JB, Grinspoon SK. Association of C-reactive protein and HIV infection with acute myocardial infarction. J Acquir Immune Defic Syndr. 2009;**51**(3):268–73.
13. Neuhaus J, Jr DRJ, Baker JV, Calmy A, Rosa A La, Kuller LH, et al. Markers of Inflammation, Coagulation and Renal Function Are Elevated in Adults with HIV Infection. J Infect Dis. 2010;**201**(12):1788–95.
14. Lang S, Mary-Krause M, Simon A, Partisani M, Gilquin J, Cotte L, et al. HIV replication and immune status are independent predictors of the risk of myocardial infarction in HIV-infected individuals. Clin Infect Dis. 2012;**55**(4):600-7.
15. Baker JV, Lundgren JD. Cardiovascular implications from untreated human immunodeficiency virus infection. Eur Heart J. 2011;**32**(8):945–51.

16. Collaboration ATC. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet. 2008;**372**(9635):293–9.
17. Rasmussen LD, Helleberg M, May M, Afzal S, Kronborg G, Larsen CS, et al. Myocardial Infarction Among Danish HIV-Infected Individuals: Population-Attributable Fractions Associated With Smoking. Clin Infect Dis. 2015;**60**(9):1415–23.
18. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/ContentFiles/Adultand Ad. Date last accessed: 20 April 2015.
19. Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier J, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. N Engl J Med. 1997;**337**(11):725–33.
20. Gulick RM, Mellors JW, Havlir D, Eron JJ, Gonzalez C MD. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. N Engl J Med. 1997;**337**(11):734–9.
21. Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet. 1998;**352**(9142):1725–30.
22. Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med. 1998;**338**(13):853–60.
23. Vittinghoff E, Scheer S, O'Malley P, Colfax G, Holmberg SD, Buchbinder SP. Combination antiretroviral therapy and recent declines in AIDS incidence and mortality. J Infect Dis. 1999;**179**(3):717–20.
24. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. Lancet. 2013;**382**(9903):1525–33.
25. Report on the global AIDS epidemic 2013. Geneva: Joint United Nations programme on HIV/AIDS, 2013. Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Global_Report_2013_en_1.pdf. Date last accessed: 4 April 2015.
26. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Date last accessed: 4 April 2015.
27. Costagliola D, Ledergerber B, Torti C, van Sighem A, Podzamczer D, Mocroft A, et al. Trends in virological and clinical outcomes in individuals with HIV-1 infection and virological failure of drugs from three antiretroviral drug classes: A cohort study. Lancet Infect Dis. 2012;**12**(2):119–27.
28. Arnedo-Valero M, Garcia F, Gil C, Guila T, Fumero E, Castro P, et al. Risk of selecting de novo drug-resistance mutations during structured treatment interruptions in patients with chronic HIV infection. Clin Infect Dis. 2005;**41**(6):883–90.
29. Wada NI, Jacobson LP, Margolick JB, Breen EC, Macatangay B, Penugonda S, et al. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. AIDS. 2015;**29**(4):463–71.
30. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011;**365**(6):493–505.

31. García F, de Lazzari E, Plana M, Castro P, Mestre G, Nomdedeu M, et al. Long-term CD4+ T-cell response to highly active antiretroviral therapy according to baseline CD4+ T-cell count. J Acquir Immune Defic Syndr. 2004;**36**(2):702–13.
32. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Available from: http://aidsinfo.nih.gov/guidelines. Date last accessed: 4 April 2015.
33. EACS. Clinical Management and Treatment of HIV Infected Adults in Europe. Version 7.1 November 2014. Available from: http://www.eacsociety.org/files/guidelines_english_71_141204.pdf. Date last accessed: 20 April 2015.
34. GeSIDA. Documento de consenso de Gesida/Plan Nacional sobre el Sida respecto al tratamiento antirretroviral en adultos infectados por el virus de la inmunodeficiencia humana (Actualización enero 2015). Available from: http://www.gesida-seimc.org/contenidos/guiasclinicas/2015/gesida-guiasclinicas-2015-tar.pdf. Date last accessed: 20 April 2015.
35. Robbins GK, De Gruttola V, Shafer RW, Smeaton LM, Snyder SW PC. Comparison of Sequential Three-Drug Regimens as Initial Therapy for HIV-1 Infection. N Engl J Med. 2003;**349**(24):2293–303.
36. Hetherington S, McGuirk S, Powell G, Cutrell A, Naderer O, Spreen B, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. Clin Ther. 2001;**23**(10):1603–14.
37. Mallal S, Phillips E, Carosi G, Molina J-M, Workman C, Tomazic J, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008;**358**(6):568–79.
38. Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet. 2008;**371**(9622):1417–26.
39. Sabin CA, Reiss P, Ryom L et al. Is there continued evidence for an association between abacavir and myocardial infarction risk? Program and abstracts of the 21st Conference on Retroviruses and Opportunistic Infections. Boston, Massachusetts, USA; 2014.
40. Mocroft A, Kirk O, Reiss P, De Wit S, Sedlacek D, Beniowski M, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS. 2010;**24**(11):1667–78.
41. Déti EK, Thiébaut R, Bonnet F, Lawson-Ayayi S, Dupon M, Neau D, et al. Prevalence and factors associated with renal impairment in HIV-infected patients, ANRS C03 Aquitaine Cohort, France. HIV Med. 2010;**11**(5):308–17.
42. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM a H, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. JAMA. 2004;**292**(2):191–201.
43. Parsonage MJ, Wilkins EGL, Snowden N, Issa BG, Savage MW. The development of hypophosphataemic osteomalacia with myopathy in two patients with HIV infection receiving tenofovir therapy. HIV Med. 2005;**6**:341–6.
44. Fux CA, Rauch A, Simcock M, Bucher HC, Hirschel B, Opravil M, et al. Tenofovir use is associated with an increase in serum alkaline phosphatase in the Swiss HIV Cohort Study. Antivir Ther. 2008;**13**(8):1077–82.

45. Arribas JR, Pozniak AL, Gallant JE, Dejesus E, Gazzard B, Campo RE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. J Acquir Immune Defic Syndr. 2008;**47**(1):74–8.
46. Reekie J, Reiss P, Ledergerber B, Sedlacek D, Parczewski M, Gatell J, et al. A comparison of the long-term durability of nevirapine, efavirenz and lopinavir in routine clinical practice in Europe: A EuroSIDA study. HIV Med. 2011;**12**(5):259–68.
47. Delaugerre C, Rohban R, Simon A, Mouroux M, Tricot C, Agher R, et al. Resistance profile and cross-resistance of HIV-1 among patients failing a non-nucleoside reverse transcriptase inhibitor-containing regimen. J Med Virol. 2001;**65**(3):445–8.
48. Boehringer-Ingelheim International Viramune product monograph, version 3.0. Ingelheim am Rhein, Germany: BoehringerIngelheim International GmbH.
49. Haas DW, Ribaudo HJ, Kim RB, Tierney C, Wilkinson GR, Gulick RM, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS. 2004;**18**(18):2391–400.
50. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutiérrez F, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. N Engl J Med. 2013;**369**(19):1807–18.
51. Sax PE, DeJesus E, Mills A, Zolopa A, Cohen C, Wohl D, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: A randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. Lancet; 2012;**379**(9835):2439–48.
52. Azijn H, Tirry I, Vingerhoets J, De Béthune MP, Kraus G, Boven K, et al. TMC278, a next-generation nonnucleoside reverse transcriptase inhibitor (NNRTI), active against wild-type and NNRTI-resistant HIV-1. Antimicrob Agents Chemother. 2010;**54**(2):718–27.
53. Vingerhoets J, Tambuyzer L, Azijn H, Hoogstoel A, Nijs S, Peeters M, et al. Resistance profile of etravirine: combined analysis of baseline genotypic and phenotypic data from the randomized, controlled Phase III clinical studies. AIDS. 2010;**24**(4):503–14.
54. Nelson M, Stellbrink H-J, Podzamczer D, Banhegyi D, Gazzard B, Hill A, et al. A comparison of neuropsychiatric adverse events during 12 weeks of treatment with etravirine and efavirenz in a treatment-naive, HIV-1-infected population. AIDS. 2011;**25**(3):335–40.
55. Molina JM, Clumeck N, Orkin C, Rimsky L, Vanveggel S, Stevens M. Week 96 analysis of rilpivirine or efavirenz in HIV-1-infected patients with baseline viral load ≤100000 copies/mL in the pooled ECHO and THRIVE phase 3, randomized, double-blind trials. HIV Med. 2014;**15**(1):57–62.
56. Périard D, Telenti A, Sudre P, Cheseaux JJ, Halfon P, Reymond MJ, et al. Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. The Swiss HIV Cohort Study. Circulation. 1999;**100**:700–5.
57. Mulligan K, Grunfeld C, Tai VW, Algren H, Pang M, Chernoff DN et al. Hyperlipidemia and insulin resistance are induced by protease inhibitors independent of changes in body composition in patients with HIV infection. J Acquir Immune Defic Syndr. 2000;**23**(1):35–43.
58. Friis-Møller N, Reiss P, Sabin CA, Weber R, Monforte A d'Arminio, El-Sadr W, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med. 2007;**356**(17):1723–35.
59. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis. 2010;**201**(3):318–30.

60. Monforte A d'Arminio, Reiss P, Ryom L, El-Sadr W, Dabis F, De Wit S, et al. Atazanavir is not associated with an increased risk of cardio- or cerebrovascular disease events. AIDS. 2013;**27**(3):407–15.
61. Lennox JL, Landovitz RJ, Ribaudo HJ, Ofotokun I, Na LH, Godfrey C, et al. Efficacy and Tolerability of 3 Nonnucleoside Reverse Transcriptase Inhibitor–Sparing Antiretroviral Regimens for Treatment-Naive Volunteers Infected With HIV-1 A Randomized, Controlled Equivalence Trial. Ann Intern Med. 2014;**167**(7):461–71.
62. Reingold J, Wanke C, Kotler D, Lewis C, Tracy R, Heymsfield S, et al. Association of HIV infection and HIV/HCV coinfection with C-reactive protein levels: the fat redistribution and metabolic change in HIV infection (FRAM) study. J Acquir Immune Defic Syndr. 2008;**48**:142–8.
63. Madden E, Lee G, Kotler DP, Wanke C, Lewis CE, Tracy R, et al. Association of antiretroviral therapy with fibrinogen levels in HIV-infection. AIDS. 2008;**22**(6):707–15.
64. Maggi P, Perilli F, Lillo A, Carito V, Epifani G, Bellacosa C, et al. An ultrasound-based comparative study on carotid plaques in HIV-positive patients vs. atherosclerotic and arteritis patients: atherosclerotic or inflammatory lesions? Coron Artery Dis. 2007;**18**(1):23–9.
65. Wang X, Chai H, Yao Q, Chen C. Molecular mechanisms of HIV protease inhibitor-induced endothelial dysfunction. J Acquir Immune Defic Syndr. 2007 Apr;**44**(5):493–9.
66. Hruz PW. Molecular mechanisms for insulin resistance in treated HIV-infection. Best Pract Res Clin Endocrinol Metab. 2011;**25**(3):459–68.
67. Hui DY. Effects of HIV protease inhibitor therapy on lipid metabolism. Prog Lipid Res. 2003;**42**(2):81–92.
68. Dressman J, Kincer J, Matveev SV, Guo L, Greenberg RN, Guerin T, et al. HIV protease inhibitors promote atherosclerotic lesion formation independent of dyslipidemia by increasing CD36-dependent cholesteryl ester accumulation in macrophages. J Clin Invest. 2003;**111**(3):389–97.
69. Sutherland JP, McKinley B, Eckel RH. The metabolic syndrome and inflammation. Metab Syndr Relat Disord. 2004;**2**(2):82–104.
70. Vasan RS. Biomarkers of cardiovascular disease: Molecular basis and practical considerations. Circulation. 2006;**113**(19):2335–62.
71. Steigbigel RT, Cooper DA, Kumar PN, Eron JE, Schechter M, Markowitz M, et al. Raltegravir with optimized background therapy for resistant HIV-1 infection. N Engl J Med. 2008;**359**(4):339–54.
72. Steigbigel RT, Cooper DA, Teppler H, Eron JJ, Gatell JM, Kumar PN, et al. Long-term efficacy and safety of Raltegravir combined with optimized background therapy in treatment-experienced patients with drug-resistant HIV infection: week 96 results of the BENCHMRK 1 and 2 Phase III trials. Clin Infect Dis. 2010;**50**(4):6005–12.
73. Gutierrez M del M, Mateo MG, Vidal F DP. Drug safety profile of integrase strand transfer inhibitors. Expert Opin Drug Saf. 2014;**13**(4):431–45.
74. Hicks C, Gulick RM. Raltegravir: the first HIV type 1 integrase inhibitor. Clin Infect Dis. 2009;48:931–9.
75. Okeke NL HC. Role of raltegravir in the management of HIV-1 infection. HIV AIDS. 2011;**3**:81–92.
76. Rockstroh JK, Lennox JL, Dejesus E, Saag MS, Lazzarin A, Wan H, et al. Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naive human immunodeficiency virus-1-infected patients: 156-week results from STARTMRK. Clin Infect Dis. 2011;**53**(8):807–16.

77. Raffi F, Jaeger H, Quiros-Roldan E, Albrecht H, Belonosova E, Gatell JM, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. Lancet Infect Dis. 2013;**13**(11):927–35.
78. Rockstroh JK, DeJesus E, Lennox JL, Yazdanpanah Y, Saag MS, Wan H, et al. Durable efficacy and safety of raltegravir versus efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. J Acquir Immune Defic Syndr. 2013;**63**(1):77–85.
79. Lennox JL, DeJesus E, Lazzarin A, Pollard RB, Madruga JVR, Berger DS, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet. 2009;**374**:796–806.
80. Landovitz RJ, Ribaudo HJ, Ofotokun I et al. Efficacy and tolerability of atazanavir, raltegravir, or darunavir with FTC/TDF: ACTG A5257. Program and abstracts of the 2014 Conference on Retroviruses and Opportunistic Infections. Boston, Massachusetts; 2014.
81. Lennox JL, Dejesus E, Berger DS, Lazzarin A, Pollard RB, Ramalho Madruga JV, et al. Raltegravir versus Efavirenz regimens in treatment-naive HIV-1-infected patients: 96-week efficacy, durability, subgroup, safety, and metabolic analyses. J Acquir Immune Defic Syndr. 2010;**55**(1):39–48.
82. Zembower TR, Gerzenshtein L, Coleman K, Palella FJ. Severe rhabdomyolysis associated with raltegravir use. AIDS. 2008;**22**(11):1382–4.
83. Dori L, Buonomini AR, Viscione M, Sarmati L, Andreoni M. A case of rhabdomiolysis associated with raltegravir use. Aids. 2010;**24**(3):473–5.
84. Masiá M, Enríquez R, Sirvent A, Gutiérrez F. Severe acute renal failure associated with rhabdomyolysis during treatment with raltegravir. A call for caution. J Infect. 2010;**61**(2):189–90.
85. Croce F, Vitello P, Dalla Pria A, Riva A, Galli M, Antinori S. Severe raltegravir-associated rhabdomyolysis : a case report and review of the literature. Int J STD AIDS. 2010;**21**(11):783–5.
86. Tsai WJ, Lee SS, Tsai HC, Sy CL, Chen JK, Wu KS, Wang YH CY. Rapid onset of rhabdomyolysis after switching to a raltegravir-based antiretroviral regimen. J Microbiol Immunol Infect. 2013;pii: S1684–**1182**(13)00034–0.
87. Isentress (raltegravir) package insert; Merck & Co., Inc., Whitehouse Station, New Jersey, 2007.
88. Justice A, Falutz J. Aging and HIV: an evolving understanding. Curr Opin HIV AIDS. 2014;**9**(4):291–3.
89. Goulet JL, Fultz SL, Rimland D, Butt A, Gibert C, Rodriguez-Barradas M, et al. Aging and infectious diseases: do patterns of comorbidity vary by HIV status, age, and HIV severity? Clin Infect Dis. 2007;**45**:1593–601.
90. Mocroft A, Reiss P, Gasiorowski J, Ledergerber B, Kowalska J, Chiesi A, et al. Serious fatal and nonfatal non-AIDS-defining illnesses in Europe. J Acquir Immune Defic Syndr. 2010;55(2):262–70.
91. Boccara F, Lang S, Meuleman C, Ederhy S, Mary-Krause M, Costagliola D, et al. HIV and coronary heart disease: Time for a better understanding. J Am Coll Cardiol Inc.2013;**61**(5):511–23.
92. Holmberg SD, Moorman AC, Williamson JM, Tong TC, Ward DJ, Wood KC, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet. 2002;**360**(9347):1747–8.

93. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab. 2007;**92**(7):2506–12.
94. Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. AIDS. 2003;**17**(17):2479–86.
95. Currier JS, Taylor A, Boyd F, Dezii CM, Kawabata H, Burtcel B, et al. Coronary heart disease in HIV-infected individuals. J Acquir Immune Defic Syndr. 2003;**33**(4):506–12.
96. El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med. 2006;**355**(22):2283–96.
97. Duprez DA, Neuhaus J, Kuller LH, Tracy R, Belloso W, De Wit S, et al. Inflammation, Coagulation and Cardiovascular Disease in HIV-Infected Individuals. PLoS One. 2012;**7**(9):e44454.
98. Hemkens LG, Bucher HC. HIV infection and cardiovascular disease. Eur Heart J. 2014;**35**(21):1373–81.
99. Friis-Møller N, Sabin CA, Weber R, d'Arminio Monforte A, El-Sadr WM, Reiss P. Combination Antiretroviral Therapy and the Risk of Myocardial Infarction. N Engl J Med. 2003;**349**(21):1993–2003.
100. Friis-Møller N, Ryom L, Smith C et al. An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons; the Data- collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. Program and abstracts of the 14th European AIDS Conference. 2013. p. Brussels, Belgium. Abstract PS1/3.
101. D:A:D Study Group, Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet. 2008;**371**(9622):1417–26.
102. Ribaudo HJ, Benson CA, Zheng Y, Koletar SL, Collier AC, Lok JJ, et al. No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: Short and long-term results from ACTG A5001/ALLRT. Clin Infect Dis. 2011;**52**(7):929–40.
103. Ding X, Andraca-Carrera E, Cooper C, Miele P, Kornegay C, Soukup M, et al. No Association of Abacavir Use With Myocardial Infarction: Findings of an FDA Meta-Analysis. J Acquir Immune Defic Syndr. 2012;**61**(4):441–7.
104. Cutrell A, Brothers C, Yeo J, Hernandez J, Lapierre D. Abacavir and the potential risk of myocardial infarction. Lancet. 2008;**371**(9622):1413.
105. Palella FJ, Gange SJ, Benning L, Jacobson L, Kaplan RC, Landay AL, et al. Inflammatory biomarkers and abacavir use in the Women's Interagency HIV Study and the Multicenter AIDS Cohort Study. AIDS. 2010;**24**(11):1657–65.
106. Bedimo RJ, Westfall AO, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events in the highly active antiretroviral therapy era. Clin Infect Dis. 2011;**53**(1):84–91.
107. Brothers CH, Hernandez JE, Cutrell AG, Curtis L, Ait-Khaled M, Bowlin SJ, et al. Risk of myocardial infarction and abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. J Acquir Immune Defic Syndr. 2009;**51**(1):20–8.
108. Cruciani M, Zanichelli V, Serpelloni G, Bosco O, Malena M, Mazzi R, et al. Abacavir use and cardiovascular disease events. Aids. 2011;**25**(16):1993–2004.
109. Strategies for Management of Anti-Retroviral Therapy/INSIGHT;D:A:D Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. AIDS. 2008;**22**(14):F17–24.

110. Hsue PY, Hunt PW, Wu Y, Schnell A, Ho JE, Hatano H, et al. Association of abacavir and impaired endothelial function in treated and suppressed HIV-infected patients. AIDS. 2009;**23**(15):2021–7.
111. Satchell CS, O'Halloran JA, Cotter AG, Peace AJ, O'Connor EF, Tedesco AF, et al. Increased Platelet Reactivity in HIV-1-Infected Patients Receiving Abacavir-Containing Antiretroviral Therapy. J Infect Dis. 2011;**204**(8):1202–10.
112. Durand M, Sheehy O, Baril J-G, Lelorier J, Tremblay CL. Association Between HIV Infection, Antiretroviral Therapy, and Risk of Acute Myocardial Infarction: A Cohort and Nested Case-Control Study Using Québec's Public Health Insurance Database. J Acquir Immune Defic Syndr. 2011;57(3):245–53.
113. Martin A, Bloch M, Amin J, Baker D, Cooper DA, Emery S, et al. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-Lamivudine: a randomized, 96-week trial. Clin Infect Dis. 2009;**49**(10):1591–601.
114. Palella FJ, Althoff KN, Moore RD et al. Abacavir use and risk for myocardial infarction in the NA-ACCORD. Program and abstracts of the 2015 Conference on Retroviruses and Opportunistic Infections; p. Seattle, Washington. Abstract 749LB.
115. Islam FM, Wu J, Jansson J, Wilson DP. Relative risk of cardiovascular disease among people living with HIV: A systematic review and meta-analysis. HIV Med. 2012;**13**(8):453–68.
116. Friis-Møller N, Thiébaut R, Reiss P, Weber R, Monforte AD, De Wit S, et al. Predicting the risk of cardiovascular disease in HIV-infected patients: the data collection on adverse effects of anti-HIV drugs study. Eur J Cardiovasc Prev Rehabil. 2010;**17**(5):491–501.
117. D'Agostino RB. Cardiovascular risk estimation in 2012: Lessons learned and applicability to the HIV population. J Infect Dis. 2012;**205**:S362–7.
118. Nordell AD, McKenna M, Borges ÁH, Duprez D, Neuhaus J, Neaton JD. Severity of cardiovascular disease outcomes among patients with HIV is related to markers of inflammation and coagulation. J Am Heart Assoc. 2014;**3**(3):e000844.
119. Hsue P, Ordovas K, Lee T GR, Michael Gotway AS. Carotid Intima-Media Thickness Among HIV-Infected Patients Without Coronary Calcium. Am J Cardiol. 2012;**109**(5):742–7.
120. Currier JS, Kendall MA, Zackin R, Henry WK, Alston-Smith B, Torriani FJ, et al. Carotid artery intima-media thickness and HIV infection: traditional risk factors overshadow impact of protease inhibitor exposure. AIDS. 2005;**19**(9):927–33.
121. Depairon M, Chessex S, Sudre P, Rodondi N, Doser N, Chave JP, et al. Premature atherosclerosis in HIV-infected individuals--focus on protease inhibitor therapy. AIDS. 2001;**15**(3):329–34.
122. Solages A, Vita JA, Thornton DJ, Murray J, Heeren T, Craven DE, et al. Endothelial function in HIV-infected persons. Clin Infect Dis. 2006;**42**(9):1325–32.
123. Van Wijk JPH, De Koning EJP, Cabezas MC, Joven J, Op't Roodt J, Rabelink TJ, et al. Functional and structural markers of atherosclerosis in human immunodeficiency virus-infected patients. J Am Coll Cardiol. 2006;**47**(6):1117–23.
124. Stein JH, Klein MA, Bellehumeur JL, McBride PE, Wiebe DA, Otvos JD, et al. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. Circulation. 2001;**104**(3):257–62.
125. Grupo de expertos del Grupo de Estudio sobre Alteraciones Metabólicas (GEAM), de la Secretaría del Plan Nacional sobre el Sida (SPNS) y del Grupo de Estudio de Sida (GeSIDA). Documento de consenso sobre alteraciones metabólicas y riesgo cardiovascular en pacientes con infección por el virus de la inmunodeficiencia humana. Enferm Infecc Microbiol Clin [Internet]. 2015;**33**(1):40.e1–40.e16.

126. Benard A, Bonnet F, Tessier J-F, Fossoux H, Dupon M, Mercie P, et al. Tobacco addiction and HIV infection: toward the implementation of cessation programs. ANRS CO3 Aquitaine Cohort. AIDS Patient Care STDS. 2007;**21**(7):458–68.
127. Tesoriero JM, Gieryic SM, Carrascal A, Lavigne HE. Smoking among HIV positive New Yorkers: Prevalence, frequency, and opportunities for cessation. AIDS Behav. 2010;**14**(4):824–35.
128. Mamary EM, Bahrs D, Martinez S. Cigarette Smoking and the Desire to Quit Among Individuals Living with HIV. AIDS Patient Care STDS. 2002;**16**(1):39–42.
129. Glass TR, Ungsedhapand C, Wolbers M, Weber R, Vernazza PL, Rickenbach M, et al. Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time: The Swiss HIV Cohort Study. HIV Med. 2006;**7**(6):404–10.
130. Petoumenos K, Worm S, Reiss P, Witt S, Monforte A, Sabin C, et al. Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D Study. HIV Med. 2011;**12**(7):412–21.
131. Riddler SA, Smit E, Cole SR, Li R, Chmiel JS, Dobs A, et al. Impact of HIV infection and HAART on serum lipids in men. JAMA. 2003;**289**(22):2978–82.
132. Calza L, Manfredi R, Chiodo F. Dyslipidaemia associated with antiretroviral therapy in HIV-infected patients. J Antimicrob Chemother. 2004;**53**(1):10–4.
133. Molina JM, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J, David N, Moyle G, Mancini M, Percival L, Yang R, Thiry A MDCST. Once-daily atazanavir/ritonavir versus twice-daily. Lancet. 2008;372(9639):646–55.
134. Mills AM, Nelson M, Jayaweera D, Ruxrungtham K, Cassetti I, Girard P-M, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. AIDS. 2009;**23**(13):1679–88.
135. Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. N Engl J Med. 2006;**354**(3):251–60.
136. Smith KY, Patel P, Fine D, Bellos N, Sloan L, Lackey P, et al. Randomized, double-blind, placebo-matched, multicenter trial of abacavir/lamivudine or tenofovir/emtricitabine with lopinavir/ritonavir for initial HIV treatment. AIDS. 2009;**23**(12):1547–56.
137. Daar ES, Tierney C, Fischl MA, Sax PE, Mollan K, Budhathoki C, et al. Atazanavir Plus Ritonavir or Efavirenz as Part of a 3-Drug Regimen for Initial Treatment of HIV-1 A Randomized Trial for the AIDS Clinical Trials Group Study A5202 Team* Background: Limited data compare once-daily options for initial therapy for HIV-1. Ann Intern Med. 2011;**154**(7):445–56.
138. Behrens G, Maserati R, Rieger A, Domingo P, Abel F, Wang H, et al. Switching to tenofovir/emtricitabine from abacavir/lamivudine in HIV-infected adults with raised cholesterol: Effect on lipid profiles. Antivir Ther. 2012;**17**(6):1011–20.
139. Young J, Weber R, Rickenbach M, Furrer H, Bernasconi E, Hirschel B, et al. Lipid profiles for antiretroviral-naive patients starting PI-and NNRTI-based therapy in the Swiss HIV Cohort Study. Antivir Ther. 2005;**10**(5):585–91.
140. Riddler SA, Haubrich R, DiRienzo AG, Peeples L, Powderly WG, Klingman KL, et al. Class-sparing regimens for initial treatment of HIV-1 infection. N Engl J Med. 2008;**358**(20):2095–106.
141. DeJesus E, Rockstroh JK, Henry K, Molina JM, Gathe J, Ramanathan S, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. Lancet. 2012;**379**(9835):2429–38.

142. Clotet B, Feinberg J, Van Lunzen J, Khuong-Josses MA, Antinori A, Dumitru I, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet. 2014;**383**(9936):2222–31.
143. Kelesidis T, Currier JS. Dyslipidemia and Cardiovascular Risk in Human Immunodeficiency Virus Infection. Endocrinol Metab Clin N Am. 2014;**43**(3):665–84.
144. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV medicine association of the infectious diseases society of America. Clin Infect Dis. 2014;**58**(1):1–10.
145. Fichtenbaum CJ, Gerber JG, Rosenkranz SL, Segal Y, Aberg JA, Blaschke T, et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. AIDS. 2002;**16**(4):569–77.
146. Bittar R, Giral P, Aslangul E, Assoumou L, Valantin MA, Kalmykova O, et al. Effects of rosuvastatin versus pravastatin on low-density lipoprotein diameter in HIV-1-infected patients receiving ritonavir-boosted protease inhibitor. Aids. 2012;**26**(14):1801–5.
147. Martínez E, Arnaiz JA, Podzamczer D, Dalmau D, Ribera E, Domingo P, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. N Engl J Med. 2003;**349**(11):1036–46.
148. Martínez E, Larrousse M, Llibre JM, Gutiérrez F, Saumoy M, Antela A, et al. Substitution of raltegravir for ritonavir-boosted protease inhibitors in HIV-infected patients: the SPIRAL study. AIDS. 2010;**24**(11):1697–707.
149. Eron JJ, Young B, Cooper DA, Youle M, DeJesus E, Andrade-Villanueva J, et al. Switch to a raltegravir-based regimen versus continuation of a lopinavir-ritonavir-based regimen in stable HIV-infected patients with suppressed viraemia (SWITCHMRK 1 and 2): two multicentre, double-blind, randomised controlled trials. Lancet. 2010;**375**(09):396–407.
150. Elzi L, Marzolini C, Furrer H, Ledergerber B, Cavassini M, Hirschel B, et al. Treatment modification in human immunodeficiency virus-infected individuals starting combination antiretroviral therapy between 2005 and 2008. Arch Intern Med. 2010;**170**(1):57–65.
151. Mallolas J, Podzamczer D, Milinkovic A, Domingo P, Clotet B, Ribera E, et al. Efficacy and safety of switching from boosted lopinavir to boosted atazanavir in patients with virological suppression receiving a LPV/r-containing HAART: the ATAZIP study. J Acquir Immune Defic Syndr. 2009;**51**(1):29–36.
152. Squires KE, Young B, Dejesus E, Bellos N, Murphy D, Zhao HH, et al. Similar efficacy and tolerability of atazanavir compared with atazanavir/ritonavir, each with abacavir/lamivudine after initial suppression with abacavir/lamivudine plus ritonavir-boosted atazanavir in HIV-infected patients. AIDS.2010;**24**(13):2019–27.
153. Squires KE, Young B, DeJesus E, Bellos N, Murphy D, Ward D, et al. ARIES 144 week results: durable virologic suppression in HIV-infected patients simplified to unboosted atazanavir/abacavir/lamivudine. HIV Clin Trials. 2012;**13**(5):233–44.
154. Ghosn J, Flandre P, Cohen-Codar I, Girard PM, Chaix ML, Raffi F, et al. Long-term (96-week) follow-up of antiretroviral-naïve HIV-infected patients treated with first-line lopinavir/ritonavir monotherapy in the MONARK trial. HIV Med. 2010;**11**(2):137–42.
155. Gatell J, Salmon-Ceron D, Lazzarin A, Van Wijngaerden E, Antunes F, Leen C, et al. Efficacy and safety of atazanavir-based highly active antiretroviral therapy in patients with virologic suppression switched from a stable, boosted or unboosted protease inhibitor treatment regimen: the SWAN Study (AI424-097) 48-week results. Clin Infect Dis. 2007;**44**(11):1484–92.

156. Sension M, Andrade Neto JL De, Grinsztejn B, Molina JM, Zavala I, González-García J, et al. Improvement in lipid profiles in antiretroviral-experienced HIV-positive patients with hyperlipidemia after a switch to unboosted atazanavir. J Acquir Immune Defic Syndr. 2009;**51**(2):153–62.
157. Wohl DA, Bhatti L, Small CB, Edelstein H, Zhao HH, Margolis DA, et al. Simplification to abacavir/lamivudine + atazanavir maintains viral suppression and improves bone and renal biomarkers in ASSURE, a randomized, open label, non-inferiority trial. PLoS One. 2014;**9**(5):e96187.
158. Ena J, Leach A, Nguyen P. Switching from suppressive protease inhibitor-based regimens to nevirapine-based regimens: A meta-analysis of randomized controlled trials. HIV Med. 2008;**9**(9):747–56.
159. Negredo E, Ribalta J, Paredes R, Ferré R, Sirera G, Ruiz L, et al. Reversal of atherogenic lipoprotein profile in HIV-1 infected patients with lipodystrophy after replacing protease inhibitors by nevirapine. AIDS. 2002;**16**(10):1383–9.
160. Dejesus E, Young B, Morales-Ramirez JO, Sloan L, Ward DJ, Flaherty JF, et al. Simplification of antiretroviral therapy to a single-tablet regimen consisting of efavirenz, emtricitabine, and tenofovir disoproxil fumarate versus unmodified antiretroviral therapy in virologically suppressed HIV-1-infected patients. J Acquir Immune Defic Syndr. 2009;**51**(2):163–74.
161. Palella FJ, Fisher M, Tebas P, Gazzard B, Ruane P, Van Lunzen J, et al. Simplification to rilpivirine/emtricitabine/tenofovir disoproxil fumarate from ritonavir-boosted protease inhibitor antiretroviral therapy in a randomized trial of HIV-1 RNA-suppressed participants. AIDS. 2014;**28**:335–44.
162. Arribas JR, Pialoux G, Gathe J, Di Perri G, Reynes J, Tebas P, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV(STRATEGY-PI): 48 week results of. Lancet Infect Dis. 2014;**14**(7):581–9.
163. Katlama C, Clotet B, Mills A, Trottier B, Molina JM, Grinsztejn B, et al. Efficacy and safety of etravirine at week 96 in treatment-experienced HIV type-1-infected patients in the DUET-1 and DUET-2 trials. Antivir Ther. 2010;**15**(7):1045-52.
164. Calin R, Paris L, Simon A, Peytavin G, Wirden M, Schneider L, et al. Dual raltegravir/etravirine combination in virologically suppressed HIV-1-infected patients on antiretroviral therapy. Antivir Ther. 2012;**17**(8):1601–4.
165. Carey D, Pett SL, Bloch M, Wand H, MacRae K, Beileiter K, et al. A randomized study of pharmacokinetics, efficacy and safety of two raltegravir plus atazanavir strategies in ART-treated adults. J Acquir Immune Defic Syndr. 2012;**60**(2):1.
166. Kozal MJ, Lupo S, DeJesus E, Molina J-M, McDonald C, Raffi F, et al. A Nucleoside- and Ritonavir-Sparing Regimen Containing Atazanavir Plus Raltegravir in Antiretroviral Treatment-Naïve HIV-Infected Patients: SPARTAN Study Results. HIV Clin Trials. 2012;**13**(3):119–30.
167. Spreen W, Williams P, Margolis D, Ford SL, Crauwels H, Lou Y, et al. Pharmacokinetics , Safety , and Tolerability With Repeat Doses of GSK1265744 and Rilpivirine (TMC278) Long-Acting Nanosuspensions in Healthy Adults. J Acquir Immune Defic Syndr. 2014;**67**(5):487–92.
168. Guiguet M, Ghosn J, Duvivier C, Meynard J-L, Gras G, Partisani M, et al. Boosted protease inhibitor monotherapy as a maintenance strategy. AIDS. 2012;**26**(18):2345–50.
169. Lambert-Niclot S, Flandre P, Valantin MA, Peytavin G, Duvivier C, Haim-Boukobza S, et al. Factors associated with virological failure in HIV-1-infected patients receiving darunavir/ ritonavir monotherapy. J Infect Dis. 2011;**204**(8):1211–6.

170. Paton N, Frcp M. Randomised controlled trial of a PI monotherapy switch strategy for long-term HIV management [Abstract 550LB]. Top Antivir Med. 2014;22(e-1):266–7.
171. Gutmann C, Cusini A, Günthard HF, Fux C, Hirschel B, Decosterd L-A, et al. Randomized controlled study demonstrating failure of LPV/r monotherapy in HIV: the role of compartment and CD4-nadir. AIDS. 2010;**24**(15):2347–54.
172. Katlama C, Valantin MA, Algarte-Genin M, Duvivier C, Lambert-Niclot S, Girard PM, et al. Efficacy of darunavir/ritonavir maintenance monotherapy in patients with HIV-1 viral suppression: a randomized open-label, noninferiority trial, MONOI-ANRS 136. AIDS. 2010;**24**(15):2365–74.
173. Arribas JR, Horban A, Gerstoft J, Fätkenheuer G, Nelson M, Clumeck N, et al. The MONET trial: darunavir/ritonavir with or without nucleoside analogues, for patients with HIV RNA below 50 copies/ml. AIDS. 2010;**24**(2):223–30.
174. Mathis S, Khanlari B, Pulido F, Schechter M, Negredo E, Nelson M, et al. Effectiveness of protease inhibitor monotherapy versus combination antiretroviral maintenance therapy: A meta-analysis. PLoS One. 2011;**6**(7):e22003.
175. Pulido F, Arribas JR, Delgado R, Cabrero E, González-García J, Pérez-Elias MJ, et al. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and two nucleosides for maintenance therapy of HIV. AIDS. 2008;**22**:F1–9.
176. Nunes EP, Santini de Oliveira M, Merçon M, Zajdenverg R, Faulhaber JC, Pilotto JH, et al. Monotherapy with Lopinavir/Ritonavir as maintenance after HIV-1 viral suppression: results of a 96-week randomized, controlled, open-label, pilot trial (KalMo study). HIV Clin Trials. 2009;**10**(6):368–74.
177. Karlström O, Josephson F, Sönnerborg A. Early virologic rebound in a pilot trial of ritonavir-boosted atazanavir as maintenance monotherapy. J Acquir Immune Defic Syndr. 2007;**44**(4):417–22.
178. Wilkin TJ, McKinnon JE, DiRienzo AG, Mollan K, Fletcher CV, Margolis DM, et al. Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy: final 48-week clinical and virologic outcomes. J Infect Dis. 2009;**199**(6):866–71.
179. Ghosn J, Flandre P, Cohen-Codar I et al. Single agent therapy with lopinavir/ritonavir durably suppresses viral replication in ARV naıve patients: IMANI II - 96week final results. Abstracts of the Forty-sixth Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC, USA; 2008.
180. Bunupuradah T, Chetchotisakd P, Ananworanich J, Munsakul W, Jirajariyavej S, Kantipong P, et al. A randomized comparison of second-line lopinavir/ritonavir monotherapy versus tenofovir/lamivudine/lopinavir/ritonavir in patients failing NNRTI regimens: The HIV STAR study. Antivir Ther. 2012;**17**(7):1351–61.
181. Reina E, Miguel RS, Larrea N, Garcia P, Napal V. Potential for simplification of HIV treatment with boosted protease inhibitor monotherapy. Int J Clin Pharm. 2012;**34**(6):911–6.
182. Moyle GJ, Sabin CA, Cartledge J, Johnson M, Wilkins E, Churchill D, et al. A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipoatrophy. AIDS. 2006;**20**(16):2043–50.
183. Fisher M, Moyle GJ, Shahmanesh M, Orkin C, Kingston M, Wilkins E, et al. A randomized comparative trial of continued zidovudine/lamivudine or replacement with tenofovir disoproxil fumarate/emtricitabine in efavirenz-treated HIV-1-infected individuals. J Acquir Immune Defic Syndr. 2009;**51**(5):562–8.

184. Campo R, Dejesus E, Bredeek UF, Henry K, Khanlou H, Logue K, et al. SWIFT: Prospective 48-week study to evaluate efficacy and safety of switching to emtricitabine/tenofovir from lamivudine/abacavir in virologically suppressed hiv-1 infected patients on a boosted protease inhibitor containing antiretroviral regimen. Clin Infect Dis. 2013;**56**(11):1637–45.
185. Martin A, Moore C, Mallon PWG, Hoy J, Emery S, Belloso W, et al. Bone mineral density in HIV participants randomized to raltegravir and lopinavir/ritonavir compared with standard second line therapy on behalf of the Second Line study team. AIDS.2013;27(15):2403–11.
186. Pozniak A, Markowitz M, Mills A, Stellbrink HJ, Antela A, Domingo P, et al. Switching to co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of non-nucleoside reverse transcriptase inhibitor with emtricitabine and tenofovir in virologically suppressed adults with HIV (STRATEGY-NNRTI): 48 week r esults of a randomised, open-label, phase 3b non-inferiority trial. Lancet Infect Dis. 2014;**14**(7):590–9.
187. Mills AM, Cohen C, Dejesus E, Brinson C, Williams S, Yale KL, et al. Efficacy and safety 48 weeks after switching from efavirenz to rilpivirine using emtricitabine/tenofovir disoproxil fumarate-based single-tablet regimens. HIV Clin Trials. 2013;**14**(5):216–23.
188. Schouten JT, Krambrink A, Ribaudo HJ, Kmack A, Webb N, Shikuma C, et al. Substitution of nevirapine because of efavirenz toxicity in AIDS clinical trials group A5095. Clin Infect Dis. 2010;**50**(5):787–91.
189. Parienti J-J, Massari V, Rey D, Poubeau P, Verdon R. Efavirenz to nevirapine switch in HIV-1-infected patients with dyslipidemia: a randomized, controlled study. Clin Infect Dis. 2007;**45**(2):263–6.
190. Waters L, Fisher M, Winston A, Higgs C, Hadley W, Garvey L, et al. A phase IV, double-blind, multicentre, randomized, placebo-controlled, pilot study to assess the feasibility of switching individuals receiving efavirenz with continuing central nervous system adverse events to etravirine. AIDS. 2011;**25**(1):65–71.
191. De Castro N, Braun J, Charreau I, Pialoux G, Cotte L, Katlama C, et al. Switch from enfuvirtide to raltegravir in virologically suppressed multidrug-resistant HIV-1-infected patients: a randomized open-label trial. Clin Infect Dis. 2009;**49**(8):1259–67.
192. LaRosa JC, He J, Vupputuri S. Effect of Statins on Risk of Coronary Disease. JAMA J Am Med Assoc.1999;**282**(24):2340–6.
193. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey SG, et al. Statins for the primary prevention of cardiovascular disease. Cochrane Database SystRev. 2013;1(1):CD004816.
194. Carr A, Hoy J, Pozniak A. The ethics of switch/simplify in antiretroviral trials: Non-inferior or just inferior? PLoS Med. 2012;**9**(7):7–10.
195. Silverberg MJ, Leyden W, Hurley L, Go AS, Quesenberry CP. Response to newly prescribed lipid-lowering therapy in patients with and without HIV infection. Ann Intern Med. 2009;**150**(5):301–13.
196. Aslangul E, Assoumou L, Bittar R, Valantin M-A, Kalmykova O, Peytavin G, et al. Rosuvastatin versus pravastatin in dyslipidemic HIV-1-infected patients receiving protease inhibitors: a randomized trial. AIDS. 2010;**24**(1):77–83.
197. Calza L, Manfredi R, Colangeli V, Tampellini L, Sebastiani T, Pocaterra D, et al. Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidaemia. AIDS. 2005;**19**(10):1051–8.

198. Antinori A, Arribas JR, Fehr J et al. Week 48 efficacy analysis of the PROTEA trial: darunavir/ritonavir monotherapy versus darunavir/ritonavir with two nucleoside analogues, for patients with HIV-1 RNA below 50 copies/mL at baseline. J Int AIDS Soc 17 (suppl 3): 24 (abstract 0423A), 2014.
199. Arribas J, Girard PM, Paton N, Winston A, Marcelin AG, Elbirt D, et al. Efficacy of PI monotherapy versus triple therapy for 1964 patients in 10 randomised trials. J Int AIDS Soc. 2014;**17**(Suppl 3):19788.
200. Arribas J, Clumeck N, Nelson M, Hill A, van Delft Y, Moecklinghoff C. The MONET trial: Week 144 analysis of the efficacy of darunavir/ritonavir (DRV/r) monotherapy versus DRV/r plus two nucleoside reverse transcriptase inhibitors, for patients with viral load <50 HIV-1 RNA copies/mL at baseline. HIV Med. 2012;**13**(7):398–405.
201. Clumeck N, Rieger A, Banhegyi D, Schmidt W, Hill A, van Delft Y, et al. 96 week results from the MONET trial: A randomized comparison of darunavir/ritonavir with versus without nucleoside analogues, for patients with hiv RNA <50 copies/ml at baseline. J Antimicrob Chemother. 2011;**66**(8):1878–85.
202. Santos JR, Moltó J, Llibre JM, Negredo E, Bravo I, Ornelas A, et al. Antiretroviral simplification with darunavir/ritonavir monotherapy in routine clinical practice: Safety, effectiveness, and impact on lipid profile. PLoS One. 2012;**7**(5):1–8.
203. Valantin MA, Lambert-Niclot S, Flandre P, Morand-Joubert L, Cabiè A, Meynard JL, et al. Long-term efficacy of darunavir/ritonavir monotherapy in patients with hiv-1 viral suppression: Week 96 results from the MONOI ANRS 136 study. J Antimicrob Chemother. 2012;**67**(3):691–5.
204. Pulido F, Pérez-Valero I, Delgado R, Arranz A, Pasquau J, Portilla J, et al. Risk factors for loss of virological suppression in patients receiving lopinavir/ritonavir monotherapy for maintenance of HIV suppression. Antivir Ther. 2009;**14**(2):195–201.
205. Arribas JR, Delgado R, Arranz A, Muñoz R, Portilla J, Pasquau J, et al. Lopinavir-ritonavir monotherapy versus lopinavir-ritonavir and 2 nucleosides for maintenance therapy of HIV: 96-week analysis. J Acquir Immune Defic Syndr. 2009;**51**(2):147–52.
206. Lambert-Niclot S, Flandre P, Valantin MA, Peytavin G, Sayon S, Morand-Joubert L, et al. Resistant minority species are rarely observed in patients on darunavir/ritonavir monotherapy. J Antimicrob Chemother. 2012;**67**(6):1470–4.
207. Cahn P, Andrade-Villanueva J, Arribas JR, Gatell JM, Lama JR, Norton M, et al. Dual therapy with lopinavir and ritonavir plus lamivudine versus triple therapy with lopinavir and ritonavir plus two nucleoside reverse transcriptase inhibitors in antiretroviral-therapy-naive adults with HIV-1 infection: 48 week results of the randomise. Lancet Infect Dis. 2014;**14**(7):572–80.
208. Gatell JM, Arribas JR, Girard PM et al. Non-inferiority of dual-therapy (DT) with lopinavir/ritonavir (LPV/r) plus lamivudine (3TC) vs triple-therapy (TT) with LPV/r plus two nucleos(t)ides (NRTIs) for maintenance of HIV-1 viral suppression: 48-week results of the OLE study. Program and abstracts of the 20th International AIDS Conference. Melbourne, Australia; 2014.
209. van Lunzen J, Pozniak A, Gatell J, Antinori A, Klauck I, Serrano O, et al. HARNESS study: ritonavir-boosted atazanavir (ATV/r)+raltegravir (RAL) switch study in virologically suppressed, HIV-1-infected patients. 20th International AIDS Conference. Melbourne, Australia; 2014.
210. Du Pasquier RA, Jilek S, Kalubi M, Yerly S, Fux CA, Gutmann C, et al. Marked increase of the astrocytic marker S100B in the cerebrospinal fluid of HIV-infected patients on LPV/r-monotherapy. AIDS. 2013;**27**(2):203-10.

211. Gisslén M, Fuchs D, Hagberg L, Svennerholm B, Zetterberg H. Cerebrospinal fluid viral breakthrough in two HIV-infected subjects on darunavir/ritonavir monotherapy. Scand J Infect Dis. 2012 Dec;**44**(12):997-1000.
212. Pérez-Valero I, González-Baeza A, Estébanez M, Montes-Ramírez ML, Bayón C, Pulido F, et al. Neurocognitive Impairment in Patients Treated with Protease Inhibitor Monotherapy or Triple Drug Antiretroviral Therapy. PLoS One. 2013;**8**(7):e69493.
213. Silva EF, Charreau I, Gourmel B, Mourah S, Kalidi I, Guillon B, et al. Decreases in inflammatory and coagulation biomarkers levels in HIV-infected patients switching from enfuvirtide to raltegravir: ANRS 138 substudy. J Infect Dis. 2013;**208**(6):892–7.
214. Pallikkuth S, Fischl MA, Pahwa S. Combination antiretroviral therapywith raltegravir leads to rapid immunologic reconstitution in treatment-naive patientswith chronic HIV infection. J Infect Dis. 2013;**208**(10):1613–23.
215. Taiwo B, Matining RM, Zheng L, Lederman MM, Rinaldo CR, Kim PS, et al. Associations of T cell activation and inflammatory biomarkers with virological response to darunavir/ritonavir plus raltegravir therapy. J Antimicrob Chemother. 2013;**68**(8):1857–61.
216. Lake J, Mccomsey GA, Hulgan T, Wanke CA, Mangili A, Walmsley SL, et al. Switch to raltegravir decreases soluble CD14 in virologically suppressed overweight women: The Women, Integrase and Fat Accumulation Trial. HIV Med. 2014;**15**(7):431–41.
217. Kelesidis T, Tran TTT, Stein JH, Brown TT, Moser C, Ribaudo HJ, et al. Changes in Inflammation and Immune Activation with Atazanavir-, Raltegravir-, DarunavirBased Initial Antiviral Therapy: ACTG 5260s. Clin Infect Dis. 2015;Epub ahead.
218. Zhou H, Jarujaron S, Gurley EC, Chen L, Ding H, Studer E, et al. HIV protease inhibitors increase TNF-⍺ and IL-6 expression in macrophages: Involvement of the RNA-binding protein HuR. Atherosclerosis. 2007;**195**:134–43.
219. Dubé MP, Shen C, Greenwald M, Mather KJ. No impairment of endothelial function or insulin sensitivity with 4 weeks of the HIV protease inhibitors atazanavir or lopinavir-ritonavir in healthy subjects without HIV infection: a placebo-controlled trial. Clin Infect Dis. 2008;**47**(4):567–74.
220. De Luca A, De Gaetano Donati K, Colafigli M, Cozzi-Lepri A, De Curtis A, Gori A, et al. The association of high-sensitivity c-reactive protein and other biomarkers with cardiovascular disease in patients treated for HIV: a nested case–control study. BMC Infect Dis. 2013;**13**:414.
221. Hunt PW, Sinclair E, Rodriguez B, Shive C, Clagett B, Funderburg N, et al. Gut Epithelial Barrier Dysfunction and Innate Immune Activation Predict Mortality in Treated HIV Infection. J Infect Dis. 2014;**210**(8):1228–38.
222. Tenorio AR, Zheng Y, Bosch RJ, Krishnan S, Rodriguez B, Hunt PW, et al. Soluble Markers of Inflammation and Coagulation but Not T-Cell Activation Predict Non-AIDS-Defining Morbid Events During Suppressive Antiretroviral Treatment. J Infect Dis. 2014;**210**(8):1248–59.
223. Young B, Vanig T, DeJesus E, Hawkins T, St Clair M, Stancil B, et al. 96-week results of a pilot study of abacavir/lamivudine and raltegravir in antiretroviral-naïve HIV-1-infected patients: the SHIELD trial. HIV Clin Trials. 2011;**12**(4):228–33.
224. McComsey GA, Kitch D, Daar ES, Tierney C, Jahed NC, Tebas P, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir-lamivudine or tenofovir disoproxil fumarate-emtricitabine along with efavirenz or atazanavir-ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG. J Infect Dis. 2011;**203**(12):1791–801.

225. Lang S, Mary-Krause M, Cotte L, Gilquin J, Partisani M, Simon A, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. Arch Intern Med. 2010;**170**(14):1228–38.
226. Obel N, Farkas DK, Kronborg G, Larsen CS, Pedersen G, Riis A, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. HIV Med. 2010;**11**(2):130–6.
227. Martínez E, Arranz JA, Podzamczer D, Loncá M, Sanz J, Barragán P, et al. A simplification trial switching from nucleoside reverse transcriptase inhibitors to once-daily fixed-dose abacavir/lamivudine or tenofovir/emtricitabine in HIV-1-infected patients with virological suppression. J Acquir Immune Defic Syndr. 2009;**51**(3):290–7.
228. Eckard AR, Jiang Y, Debanne SM, Funderburg NT, McComsey GA. Effect of 24 Weeks of Statin Therapy on Systemic and Vascular Inflammation in HIV-Infected Subjects Receiving Antiretroviral Therapy. J Infect Dis. 2014;**209**:1156–64.
229. Van Leth F, Phanuphak P, Stroes E, Gazzard B, Cahn P, Raffi F, et al. Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naive patients infected with HIV-1. PLoS Med. 2004;**1**(1):e19.
230. FDA Crestor Prescribing Information. 2014 [updated July 08].
231. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;**359**(21):2195–207.
232. Sharif A, Ravindran V, Moore R, Dunseath G, Luzio S, Owens D, et al. The effect of rosuvastatin on insulin sensitivity and pancreatic beta-cell function in nondiabetic renal transplant recipients. Am J Transplant. 2009;**9**:1439–45.
233. Kostapanos MS, Milionis HJ, Agouridis A-D, Rizos C V, Elisaf MS. Rosuvastatin treatment is associated with an increase in insulin resistance in hyperlipidaemic patients with impaired fasting glucose. Int J Clin Pract. 2009;**63**(9):1308–13.
234. Reynes J, Trinh R, Pulido F, Soto-Malave R, Gathe J, Qaqish R, et al. Lopinavir/Ritonavir Combined with Raltegravir or Tenofovir/Emtricitabine in Antiretroviral-Naive Subjects: 96-Week Results of the PROGRESS Study. AIDS Res Hum Retroviruses. 2013;**29**(2):256–65.
235. Taiwo B, Zheng L, Gallien S, Matining RM, Kuritzkes DR, Wilson CC, et al. Efficacy of a nucleoside-sparing regimen of darunavir/ritonavir plus raltegravir in treatment-naive HIV-1-infected patients (ACTG A5262). AIDS. 2011;**25**:2113–22.
236. Raffi F, Babiker AG, Richert L, Molina J-M, George EC, Antinori A, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir–emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ ANRS143 randomised non-inferiority trial. Lancet. 2014;**384**(9958):1942–51.
237. Casado JL, Bañón S, Rodriguez MA, Moreno A, Moreno S. Efficacy and pharmacokinetics of the combination of etravirine plus raltegravir as novel dual antiretroviral maintenance regimen in HIV-infected patients. Antiviral Res. 2015;**113**:103–6.
238. Margolis DA, Brinson CC, Eron JJ et al. GSK1265744 and rilpivirine as two drug oral maintenance therapy: LAI116482 (LATTE) week 48 results. Program and abstracts of the 2014 Conference on Retroviruses and Opportunistic Infections. Boston, Massachusetts, USA; 2014.

239. Lee FJ, Amin J, Bloch M. Skeletal Muscle Toxicity Associated With Raltegravir-Based Combination Antiretroviral Therapy in HIV-Infected Adults. J Acquir Immune Defic Syndr. 2013;**62**(5):525–33.
240. Madeddu G, De Socio GVL, Ricci E, Quirino T, Orofino G, Carenzi L, et al. Muscle symptoms and creatine phosphokinase elevations in patients receiving raltegravir in clinical practice: Results from the SCOLTA project long-term surveillance. Int J Antimicrob Agents. 2015;45(3):289–94.
241. Squires KE, Bekker L-G, Eron JJ, Cheng B, Rockstroh JK, Marquez F, et al. Safety, Tolerability, and Efficacy of Raltegravir in a Diverse Cohort of HIV-Infected Patients: 48-Week Results from the REALMRK Study. AIDS Res Hum Retroviruses. 2013;**29**(6):859–70.
242. Calza L, Danese I, Colangeli V, Vandi G, Manfredi R, Girometti N, et al. Skeletal muscle toxicity in HIV-1-infected patients treated with a raltegravir-containing antiretroviral therapy: a cohort study. AIDS Res Hum Retroviruses. 2014;**30**(12):1162–9.
243. Grinsztejn B, De Castro N, Arnold V, Veloso VG, Morgado M, Pilotto JH, et al. Raltegravir for the treatment of patients co-infected with HIV and tuberculosis (ANRS 12 180 Reflate TB): A multicentre, phase 2, non-comparative, open-label, randomised trial. Lancet Infect Dis. 2014;14(6):459–67.
244. Fourati S, Charpentier C, Calvez V, Flandre P, Marcelin A-G, Chemother JA. Cross-resistance to elvitegravir and dolutegravir in 502 patients failing on raltegravir: a French national study of raltegravir-experienced HIV-1-infected patients. J Antimicrob Chemother. 2015;**11**(20):2–4.

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