Switching antiretroviral therapy to minimize metabolic complications

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Abstract

Advances in HIV therapy have made living with HIV for decades a reality for many patients. However, antiretroviral therapy has been associated with multiple long-term complications, including dyslipidemia, fat redistribution, insulin resistance and increased cardiovascular risk. As newer agents with improved metabolic profiles have become available, there is growing interest in the safety and efficacy of switching ART as a strategy to reduce long-term complications. This article reviews recently published data on switching ART to minimize the contributions of specific agents to these complications.

Keywords

antiretroviral therapy; cardiovascular disease; etravirine; insulin resistance; lipid abnormalities; maraviroc; metabolic complications; protease inhibitors; raltegravir

Since the advent of HAART, rates of AIDS-related deaths have declined in industrialized countries, while other causes of death, including cardiovascular disease (CVD) and non-AIDS malignancies, have increased among HIV-infected patients [1–4]. This trend, however, does not mirror the mortality profile of the general population. In a study of 29,935 HIV-infected patients in Europe and North America, non-AIDS mortality exceeded that of the general population in HIV-infected patients surviving the first 6 months of antiretroviral therapy (ART) [1].

HIV-infected patients appear to be at increased risk of CVD, a finding that has been linked to both HIV infection and ART [5–12]. The risk attributable to ART may be due (in part) to both individual antiretroviral agents and the complications they cause, which include insulin resistance, proatherogenic lipid profiles, and changes in subcutaneous and visceral fat distribution [5,6,8,10,13–16]. As a result, optimizing ART to minimize CVD risk and other

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complications has become an important component of the long-term management of HIV infection.

Standard therapies for disturbances such as insulin resistance and central fat accumulation in the non-HIV-infected population have been suboptimal when employed in the setting of HIV- and ART-related metabolic dysregula-tion, complicating the development of treatment strategies. Minimizing these complications via selection of a metabolically optimized initial ART regimen, or switching regimens to minimize current complications may be a legitimate tactic for the long-term management of HIV infection.

As we learn more about the metabolic pro-files of newer antiretroviral agents, there will be increased interest in the role of switching ART to improve metabolic disturbances. Well-designed, prospective, randomized trials provide the best evidence to help evaluate the possible benefits of a change in one or more components of the ART regimen. However, the first priority should continue to be maintaining an undetectable HIV-1 RNA level in the context of any ART switches.

Much of the published data on switching antiretroviral classes or agents are limited to the nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) classes of agents. However, as new classes of agents (including integrase inhibitors and entry inhibitors) have emerged, there are accumulating data on how these agents may be used to minimize long-term, ART-associated metabolic complications.

This article focuses on switching ART to minimize the common metabolic complications associated with cardiovascular risk. Within each section, data published on the outcomes of different switch strategies in the last 5 years is reviewed. Priority is given to randomized, prospective studies specifically designed to evaluate the effects of switching ART on metabolic outcomes. However, where these data are lacking, data from switch studies designed to examine virologic efficacy and/or observational cohort data are mentioned (in this article, only prospective switch studies are include in Tables 1, 2, and 3). The data presented are varied with respect to the patient populations enrolled and the measurement and reporting of changes in metabolic parameters, making comparisons difficult. To facilitate comparison, common themes are highlighted and data is presented in a consistent format where possible (absolute or percent change values were calculated from the published data when not already present). Strict parameters for clinically meaningful improvements in HIV-and/or ART-induced metabolic abnormalities are lacking, and expectations and goals must be highly individualized. However, the benefit of improvement probably increases with the severity of the metabolic perturbation, and guidelines such as those of the National Cholesterol Education Program can be used to aid clinical decision-making.

The article is divided into sections focused on specific metabolic end points, including lipid abnormalities, lipoatrophy and lipohypertrophy, insulin resistance, and overall cardiovascular risk. Studies that evaluated multiple end points or agents are referenced in more than one section (where applicable). In addition, sections are broken down into studies designed to: switch within a class of agents, avoid a single class of agents (such as PIs), or avoid multiple classes of agents (such as PIs and NRTIs).

Minimizing lipid abnormalities

Lipid abnormalities, such as increased triglyc-erides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDLc), and decreased high-density lipoprotein cholesterol (HDLc), have been demonstrated in HIV-infected patients on or initiating ART [7,17–19]. Certain agents, such as lopinavir/ritonavir and the thymidine analog NRTIs, have

specifically been associated with these changes. The available strategies for minimizing proatherogenic lipid changes include switching within and between ART classes to avoid the agents most associated with dyslipidemia. A summary of recent data on lipid level changes following a switch in ART is available in Table 1.

Switching within classes

Protease inhibitors—In the last 2 years, substantial data have been published demonstrating differences in lipid profiles among individual PIs, primarily in patients switching from lopinavir/rito-navir to atazanavir/ritonavir or unboosted atazanavir. In a study of 15 HIV-infected men and women with dyslipidemia and/or hyperinsulinemia, switching from lopina-vir/ritonavir to atazanavir/ritonavir resulted in significant mean improvements in TG (−155 mg/dl, 51%, between-group p = 0.02) and TC (−44 mg/dl; 20%; between-group p = 0.01) without improvements in LDLc or HDLc over a 6-month period [20]. In the SABAR study, significant improvements in median TC (−25 mg/dl, −12%, between-group p = 0.009), non-HDLc (−27 mg/dl; −16%; between-group p = 0.014), and TG (−58 mg/dl, −23%, between-group p = 0.013) were observed after 24 weeks in subjects with baseline elevations in LDLc or TG who switched to boosted atazanavir from another PI. Decreases in median LDLc were also observed, although these did not reach statistical significance [21].

In the A1424–067 study of subjects with baseline LDLc elevations, significant improvements were seen in subjects who switched to unboosted atazanavir compared with subjects remaining on other ritonavir-boosted or unboosted PIs (mean change −24 mg/dl, −15%, between-group p < 0.0001) [22]. In a similarly designed study, subjects with elevated LDLc had more significant mean improvements in all lipid parameters after switching to unboosted atazanavir, and only subjects switching to atazanavir experienced improvements in TG and HDLc [23]. Finally, in the ARIES study, subjects who discontinued ritonavir after achieving virologic suppression on abacavir/lamivudine (3TC) plus atazanavir/ ritonavir, demonstrated improvements in median TC (−13 mg/dl [−7%] vs 9 mg/dl [5%], between-group p < 0.001), LDLc (−8 mg/dl [−8%] vs 6 mg/dl [6%], between-group p = 0.006), and TG (−40 mg/dl [−25%)] vs −7 mg/dl [−4%], between group p < 0.001) compared with subjects continuing atazanavir/ritonavir. Importantly, unboosted atazanavir demonstrated noninferi-ority to atazanavir/ ritonavir after 84 weeks in maintaining virologic suppression [24].

Although no prospective switch data are available, darunavir, the most recently FDA-approved PI, has demonstrated similar TG and TC changes to atazanavir [25,26], smaller mean increases in TG than lopinavir/ritonavir in treatment-experienced patients receiving optimized background therapy in the TITAN study [27], and smaller median increases in TG and TC than lopinavir/ritonavir (each in combination with tenofovir/emtricitabine [FTC]) in treatment-naive subjects in the ARTEMIS trial [28]. Head-to-head comparisons are required to further elucidate the potential benefits of switching to darunavir from PIs known to induce less favorable lipid profiles.

In a meta-analysis of boosted PI use in treatment-naive subjects, subjects receiving boosted saquinavir, atazanavir or darunavir (group 1) had smaller increases in mean TC (magnitude not reported; p < 0.039) and TG (difference between groups 39 mg/dl; 31%; p < 0.0001) than in subjects on ritonavir-boosted lopina-vir or fosamprenavir (group 2). No significant differences in LDLc or HDLc were observed between individual PIs, although a trend towards greater LDLc elevations was seen for group 2 [26].

In summary, among PIs, improvements in TC and TG have been most widely documented with a switch to atazanavir therapy, although data exist supporting the potential for benefit from switching to saquinavir or darunavir.

Nucleoside reverse transcriptase inhibitors—Recent data demonstrates some benefit of switching from the thymidine analog NRTIs (zidovudine [AZT] and stavudine [d4T]) to tenofovir-containing regimens. The predominant changes observed in subjects who switched to tenofovir or FTC from other NRTI backbones were improved TC and/or TG levels [29–34], although improvements in LDLc have also been observed [26,29]. In a recent meta-analysis, subjects receiving combinations of AZT, d4T, abacavir or 3TC had more severe mean elevations of TC (magnitude not reported; $p < 0.0001$), TG (23 mg/dl; $p < 0.001$) and LDLc (10 mg/dl; $p = 0.001$), and less improvement in HDLc than those receiving tenofo-vir/FTC (difference in percentage change but not absolute change, magnitude not reported; $p < 0.001$) [26].

In the STEAL study, virologically suppressed subjects were switched from their current NRTIs to fixed-dose tenofovir/FTC or abacavir/3TC, while remaining on their PI or non-nucleoside reverse transcriptase inhibitor (NNRTI). After 96 weeks, subjects in the abacavir/3TC group had significantly greater TC (15.4 vs −3.9 mg/dl; 8 vs −2%; $p < 0.001$). A trend towards increased LDLc (7.7 vs 0.0 mg/dl; 6 vs 0%; $p = 0.06$) in the abacavir/3TC group, and improved TG in the tenofovir/emtricitabine group (17.7 vs −17.7 mg/dl; 9 vs −9%; $p = 0.08$) was observed. HDLc declined in the FTC group (0.0 vs −3.9 mg/dl; 0 vs −8%; $p = 0.004$) [35].

Non-nucleoside reverse transcriptase inhibitors—Previous data exists on switching within the NNRTI class of agents for a number of ART-associated complications, including dyslipid-emia; however, there are few studies from the past 5 years. This is likely due to a combination of factors, including the small number of agents, the recommendation of efavirenz as a first-line agent for HIV treatment by many agencies, data supporting the superiority of efa-virenz over nevirapine [36,37], concerns for hepa-totoxicity with nevirapine and the low genetic barrier to resistance seen in first-generation NNRTIs.

In the SIROCCO study, patients with elevated LDLc who switched from efavirenz to nevirapine experienced a statistically significant decline in mean LDLc (difference between groups −13.1 mg/dl, −8%; p value for nevirapine in multivariable ana lysis $p < 0.04$) and no excess adverse events after 52 weeks [38].

Etravirine, a second-generation NNRTI, has a higher barrier to resistance, but is approved only for the treatment of ART-experienced patients, making head-to-head comparisons difficult. However, etravirine does not appear to have a significant effect on lipids [39]. Future studies are required to confirm this finding before switching from efavirenz to etravirine could become an accepted strategy for minimizing efavirenz-associated lipid abnormalities.

Switching between classes

PI-sparing regimens—Early PI-sparing interventions primarily focused on a switch from PI- to NNRTI-based therapy. These results are well known and will be only briefly summarized in this article. In general, switching from a PI to a NNRTI resulted in either nonsignificant changes or an improvement in lipid parameters [40–43].

The SWITCHMRK 1 and 2 studies assessed the safety and efficacy of switching from lopinavir/ritonavir to raltegravir while continuing a stable NRTI backbone. Although these studies were closed early due to the apparent failure of raltegravir to meet noninferiority

criteria for virologic efficacy, impressive improvements in mean TC (−28.0 mg/dl, −13%), mean non-HDLc (−25.0 mg/dl, −15.0%), and median TG (−84.4 mg/dl, −42.2%) were observed in subjects 12 weeks after switching to raltegravir (all p < 0.0001 vs control). No differences in mean LDLc or HDLc were observed. TC: HDLc ratios were not reported [44]. A prior history of virologic failure appeared to be associated with a higher risk of virologic breakthrough during this study.

In the SPIRAL study, subjects on any ritona-vir-boosted PI were randomized to either switch to raltegravir or continue PI. significant mean percent changes from baseline were observed in the raltegravir group for all individual lipid levels (TC −11%; LDLc −6%; HDLc −3%; TG −22%; all p < 0.0001 vs control) and the TC: HDLc ratio (−4.85%, p < 0.05 vs control) after 48 weeks, and fewer patients in the switch group required lipid-lowering therapy at the end of the follow-up period (absolute change values were not calculated as median baseline values and mean percent changes were reported). These improvements in lipids occurred early, and were maintained throughout the study. In a subgroup analysis, improvements in lipids were significant in the group switching from lopinavir/ ritonavir but not atazanavir/ritonavir, although the study was not powered for this endpoint. Of note, although this study was smaller than the SWITCHMRK studies (n = 273 vs 702), switch to raltegravir in the SPIRAL study was not associated with an increased incidence of virologic failure [45].

NRTI-sparing regimens—While there has been great interest in minimizing ART-associated toxicities by providing NRTI-sparing regimens to patients, it is unclear whether this may be an option for lipid management. The study group ACTG 5152s compared a 3TC-containing NRTI backbone plus efavi-renz or lopinavir/ritonavir to the NRTI-sparing regimen of efavirenz plus lopinavir/ritonavir. Subjects in the NRTI-sparing arm demonstrated significantly larger median increases in LDLc than either NRTI-containing arm (p < 0.01), suggesting an additive effect on LDLc for efavi-renz and lopinavir/ritonavir. A similar trend was seen for HDLc (p = 0.069), although, unlike elevations in LDLc, the effect on HDLc was metabolically desirable [46].

In the NONUKEer trial, subjects with lipoat-rophy were randomized to continue therapy or switch from an NRTI-containing regimen to an NNRTI plus PI regimen. In the switch group, an increase in mean TG (133.6 ± 325.7 mg/dl, between-group p = 0.002) was demonstrated at week 48 that did not persist at week 96. Mean LDLc was more favorable in the NRTI group (−12.7 vs 3.1 mg/dl; p = 0.045) at week 96 (but not at week 48), and an increase in mean HDLc was seen only at week 96 for the NRTI-sparing group (−0.8 vs 4.6 mg/dl, between group p = 0.025). Similar numbers of subjects in each group (9/50 and 8/50) required lipid-lowering therapy by week 96 [47].

In a similar study design, ACTG protocol A5110 switched subjects that had developed lipoatrophy on a AZT- or d4T–containing regimen to lopinavir/ritonavir plus nevirapine. Median TC and TG increased by 24 mg/dl (12%, p < 0.001) and 56 mg/dl (21%, no within-arm p-value reported), respectively. Median HDL increased by 3 mg/dl (p = 0.01) [48]. While NRTI-sparing switch studies involving newer agents such as raltegravir and etravirine have not yet been performed, these data suggest that switching a NRTI to a PI (particularly lopinavir/ritonavir) plus NNRTI may not be a viable option for improving lipid parameters in HIV-infected patients.

NNRTI-sparing regimens—To date, there are no prospective switch studies that include a change to maraviroc. This is probably due to the fact that, while HIV-1 proviral DNA sequencing has been shown to effectively determine tropism in virologically suppressed patients [49,50], routine testing for R5 receptor-using virus is not yet widely available.

However, data from studies using the CCR5 inhibitor maraviroc provide support for the potential metabolic advantages of this new agent. The MERIT study was a double-blind, randomized, controlled trial of AZT/3TC in combination with either maraviroc or efavirenz for antiret-roviral-naive patients with R5-tropic virus. At week 48, greater median increases in TG (20.8 vs −9.0 mg/dl; p = 0.0002), TC (35.9 vs 2.0 mg/dl), LDLc (20.7 vs −9.0 mg/dl), and HDLc (13.5 vs 6.9 mg/dl) were seen in the efavirenz arm (TC, LDLc, HDLc; p < 0.0001). Median TC: HDLc ratio decreased more in the maraviroc arm (−0.54 vs −0.43, p = 0.005). Greater numbers of subjects receiving efavirenz developed LDLc levels meeting National Cholesterol Education Program treatment thresholds (efavirenz vs maravi-roc: TC ≥ 200 mg/dl; 31.4 vs 8.2%; LDLc ≥160 mg/dl; 9.0 vs 0.9%; LDLc ≥ 130 mg/dl; 21.5 vs 4.6%; all p < 0.0001, subjects with baseline values exceeding these cut-offs excluded). These findings suggest maraviroc may be more lipid-neutral than efavirenz [51,52]. It is not known whether the lipid-neutral effects of maraviroc seen in the MERIT study would translate to an improvement in lipids for patients that have already developed hy perlipidemia on another ART regimen.

In a study of 563 treatment naive subjects randomized to tenofovir/FTC with either ralte-gravir or efavirenz, subjects on raltegravir but not efavirenz demonstrated minimal changes in mean TC, LDLc, HDLc (p < 0.001 vs efavirenz), and TG (p = 0.001) after 96 weeks. There was no difference in TC:HDLc ratio was seen between the two groups [53].

Multiple class-sparing regimens—In a 48-week study of triple-class experienced patients, 28 subjects with R5-tropic virus who were failing their current antiretroviral regimens were switched to a regimen of maraviroc, raltegravir, and etravirine. High rates of viro-logic suppression were observed. Regarding lipids, a significant increase in HDLc was observed (2 mg/dl, p = 0.027), four out of five subjects receiving fibrate therapy at baseline discontinued the fibrate while on study secondary to improved TG levels, and no subject required initiation of lipid-lowering therapy [54]. Larger studies are needed to confirm these findings, which suggest a more neutral effect on lipids for this combination of antiretroviral agents than those of more traditional regimens.

Minimizing lipodystrophy

Lipoatrophy and lipohypertrophy are associated with multiple metabolic derangements in the setting of HIV infection and ART. In addition, visceral adipose tissue (VAT) has been linked to CVD in HIV-infected men irrespective of BMI or waist girth [55]. In addition to the metabolic consequences, lipodystrophic changes can significantly affect quality of life and the desire to continue strict medication adherence for some patients. Therefore, minimizing these changes when selecting an antiretroviral regimen has numerous potential benefits. Recent data on changes in fat distribution following a switch in ART are available in Table 2.

Switching within classes

Protease inhibitors—An improvement in mean VAT volume was demonstrated in subjects with dyslipidemia and/or hyperinsulinemia who switched from lopinavir/ ritonavir to atazanavir/ritonavir (−25 cm^2, 22%; p = 0.047) [20]. The individual effects of other PIs on fat redistribution are less clear. In a study of 140 treatment-naive subjects, Carr and colleagues demonstrated similar median increases in limb fat mass and decreases in median VAT volume in subjects randomized to tipranavir/rito-navir or lopinavir/ritonavir, each in combination with tenofovir/3TC [56].

Nucleoside reverse transcriptase inhibitors—Data to support switching NRTIs to improve lipodystrophy has centered upon switching from the thymidine analogs to newer

agents including tenofovir and emtricitabine. In the SWEET study, subjects were randomized to receive tenofovir/FTC versus continued AZT/3TC, each with efavirenz. Subjects switching to FTC experienced a mean increase in limb fat by dual energy x-ray absorptio metry. Those continuing AZT/3TC lost limb fat, resulting in a statistically significant difference between the two groups after 48 weeks (mean between-group difference 448 g, p = 0.025; mean within-group change for switch group 0.26 kg, 4%; p = 0.054). **No statistically sig**-nificant differences were observed between or within groups for trunk or whole body fat, and total body fat increased for both groups (tenofovir/FTC mean = 393 g, AZT/3TC mean = 299g). However, fat gain in the teno-fovir/FTC arm occurred predominantly in the limbs (mean change from baseline 261 g), whereas subjects continuing AZT/3TC experienced greater increases in trunk fat (mean change from baseline 358 g). All fat redistribution occurred without significant changes in weight or BMI [30].

In the LIPOTEST trial, subjects with lipoat-rophy experienced increased median malar fat thickness (0.8 mm; 25%; p < 0.001) and total fat mass (3.9 kg; 21%; p < 0.001) following a switch from d4T to tenofovir [33]. Similarly, studies by Madruga *et al.* and Milinkovic *et al.* demonstrated significant increases in limb fat in subjects on d4T who switched to tenofo-vir (mean 1.3 kg [29%] and median 402 g, respectively) [31,32].

In ACTG A5142, less lipoatrophy was observed with tenofovir (9%) than d4T (42%) or AZT (27%; p < 0.001 for tenofovir vs other NRTI; p = 0.038 d4T vs AZT) when controlling for other antiretroviral agents and confounding factors. A median of 2.2 kg trunk fat was gained for all subjects, irrespective of NRTI choice [57]. In ACTG A5110, switching from AZT or d4T to abacavir resulted in a 15% median improvement in VAT (absolute change 18.3 cm^2, p = 0.04), and an 18% median improvement in subcutaneous thigh fat (absolute change 2.9 cm^2; p < 0.01) [48]. Together, these data suggest that tenofovir and/or abaca-vir may be less likely to cause lipoatrophy than thymidine analog NRTIs.

Non-nucleoside reverse transcriptase inhibitors—Few data exist that directly compare the individual effects of NNRTIs on lipodystrophy. Comparative studies are needed, particularly given the increased use of etravirine and recommendation of efavirenz as a first-line agent in many settings.

Switching between classes

PI-sparing regimens—Data from the Spanish Lipodystrophy Group suggest no benefit to switching from a PI to nevi-rapine on anthropometric measurements among patients with lipodystrophy [58]. However, further study is needed, particularly on switching from PIs to agents such as raltegravir, etravirine and maraviroc.

NRTI-sparing regimens—In the NONUKE trial, subjects with lipoat-rophy who switched from a NRTI-containing regimen to a NNRTI plus PI regimen experienced increased subcutaneous thigh fat by computed tomography (total 48-week NRTI-sparing vs NRTI mean difference = 41 cm^3, 12%, p = 0.004; total 96-week mean difference 109 cm^3, 30%, p = 0.001), corresponding to 12 and 30% increases in overall fat volume at weeks 48 and 96, respectively, in the NRTI-sparing arm. specifically regarding limb fat, only subjects discontinuing a thymidine analog had significant improvements in limb fat over the 96-week follow-up period. A trend towards improved subcutaneous abdominal fat was seen in the switch group (p = 0.088), and subcutaneous adipose tissue:total fat ratios also improved (p = 0.007), but no improvement in VAT or anthropomorphic measurements was seen after 48 and 96 weeks [47].

In ACTG A5110, subjects with self-reported lipoatrophy who switched from a AZT or d4T–containing regimen to lopinavir/ritonavir plus nevirapine experienced a 17% median improvement in subcutaneous thigh fat (absolute change 3.2 cm^2; p < 0.01) [48].

In the MONOI-ANRS 136 study, subjects were randomized to continue darunavir/ritonavir plus a NRTI backbone, or switch to ritonavir-boosted darunavir alone. Despite the virologic noninferiority of darunavir monotherapy, subjects in the monotherapy group demonstrated a 0.34 kg (7%) median increase in limb fat over 48 weeks, whereas subjects remaining on triple-drug therapy experienced a median decrease in limb fat (−0.02 kg, 0.4%), with an overall significant between arm difference (p = 0.011). In addition, 11% of subjects receiving nonthymidine analog NRTI therapy experienced more than 20% loss of limb fat versus 1% of subjects receiving daru-navir alone (p = 0.04). No between group difference was noted for trunk fat volume or the percentage of subjects with protocol-defined lipohypertrophy (>20% gain of trunk fat) [59].

These data suggest that NRTI-sparing regimens could be an alternative for patients with peripheral lipoatrophy, and/or that NRTI-sparing regimens could be used as first-line agents to prevent lipoatrophy. However, further studies of non-NRTI combination ART are necessary to establish whether these findings persist in the setting of specific regimens that also maintain acceptable rates of virologic control.

NNRTI-sparing regimens—In a study of treatment naive subjects initiating tenofovir/FTC with raltegravir or efavirenz, similar mean amounts of limb, trunk and total body fat gain were seen in both groups. Lipoatrophy (≥20% loss of appendicular fat) was uncommon for both raltegravir- and efavirenz-based regimens [53]. Similar mean increases in visceral and subcutaneous fat have also been described in subjects initiating unboosted atazanavir or efavirenz therapy, each in c ombination with AZT/3TC [60].

In ACTG A5142, less lipoatrophy was observed in subjects initiating lopinavir/ritonavir than efavirenz (17% vs 32%; odds ratio [OR] for efavirenz vs lopinavir/ritonavir = 2.66), irrespective of other concomitant antiretroviral agents and despite similar total bodyweight gain in both groups (mean 3.6 kg, 5%) [57]. However, it is unknown whether switching to lopinavir/rito-navir from efavirenz would improve lipoatrophy in subjects with pre-existing fat loss. In addition, this benefit was offset by greater lipid changes in the lopinavir/ritonavir arm [57]. Given the other metabolic perturbations seen with PIs, improved knowledge of the effects of the integrase and entry inhibitors will be important to understanding whether NNRTI-sparing regimens are viable choices for the prevention of lipodystrophy and other metabolic complications of ART.

Multiple class-sparing regimens—In a study of 28 triple-class experienced subjects with R5-topic virus, Nozza *et al.* observed an increase in BMI (1.5 units, 7%; p = 0.0002) and waist circumference (2.8 cm, 3%; p = 0.002) over 48 weeks in subjects switching to a regimen of maraviroc, raltegravir and etravirine. These changes were associated with improvements in serum lipid levels, but no change was observed in glucose or insulin levels [54], suggesting that the increase in BMI and waist circumference could refect improved nutrition/decreased wasting following improved virologic control. This finding warrants further investigation, and specific sites f fat redistribution should be analyzed in patients receiving these agents before claims regarding the frequency of lipodystrophy with this regimen can be made.

Minimizing insulin resistance

Both insulin resistance and frank diabetes are important potential complications of ART. Insulin resistance is a component of the metabolic syndrome, and is known to be associated with the development of atherosclerotic vascular disease. Frank diabetes is considered a myocardial infarction equivalent in predicting the risk of future cardiovascular events. Preventing the development of insulin resistance in patients with normal blood glucose and/ or preventing progression to frank diabetes in patients with baseline glucose elevations or insulin resistance is important to minimizing cardiovascular risk in HIV-infected patients.

While the development of insulin resistance has been associated with ART, quantifying insulin resistance and directly comparing the effects of individual agents on insulin resistance has proved more challenging. The variability of insulin assays and inconsistent use of scoring systems or surrogate measures of insulin sensitivity confound data, and make cross-study comparison difficult. Despite these obstacles, determining agent-specific effects of ART on insulin resistance remains an important challenge in the management of ART-associated complications.

Switching within classes

Protease inhibitors—Conflicting results have been reported on the contribution of specific PIs to the development of insulin resistance in patients on ART. In 15 HIV-infected subjects with baseline dys-lipidemia and/or hyperinsulinemia, Stanley and colleagues demonstrated improved mean fasting glucose levels and anterior thigh muscle glucose uptake 24 weeks following a switch to atazanavir/ ritonavir from lopinavir/ritonavir (serum glucose −3 mg/dl [3%], between-group treatment effect −15 mg/dl; p = 0.002; anterior thigh glucose uptake 13.7 ¼mol/kg/min [105%], between-group treatment effect 18.2 ¼mol/kg/min; p = 0.035) [20]. Similarly, Busti and colleagues reported a significant improvement in insulin resistance (+28%, p = 0.008, as measured by the euglycemic clamp method) in nine subjects switching from any other PI to atazanavir/ r itonavir [61].

Contrary to these findings, the SABAR study did not show improvements in median serum glucose or insulin levels following 75 mg oral dextrose challenge, or in the homeostasis model assessment of insulin resistance (HOMA-IR) in 26 patients switching from another PI to boosted atazanavir [21]. While interpretation of data from some studies has been limited by their size, larger studies have been performed. In the AI424–067 trial, no improvement in mean fasting glucose levels was seen in 246 subjects switching from another PI to unboosted atazanavir [22]. The percentage of subjects with baseline insulin resistance in each of these trials is unknown, but would be useful in judging the magnitude of improvement, if any, for subjects with and without insulin resistance that switch PIs.

Nucleoside reverse transcriptase inhibitors—There are minimal data on the effects of switching within the NRTI class on insulin resistance. However, in ACTG A5110, no significant change in median glucose or insulin levels occurred in patients switched from a thymidine analog to abacavir [48].

Non-nucleoside reverse transcriptase inhibitors—Little data exists on differences in rates of insulin resistance among members of the NNRTI class. Based on studies of PI- and NRTI-sparing regimens containing efavirenz or nevirapine, use of a NNRTI is associated with stable or improved insulin resistance compared with other antiretro-viral agents [62–64]. However, head-to-head studies are needed to document specific differences among members of this class, particularly efavirenz and etravirine, as well as switch studies to determine whether or not switching to a NNRTI might have an effect on insulin sensitivity.

Switching between classes

PI-sparing regimens—In the SWITCHMRK and SPIRAL studies, no grade 3 or 4 elevations of fasting glucose were documented in the raltegravir or the PI arms [44,45]. These studies were not primarily designed to examine improvement in insulin resistance; however, given these findings, assessment of insulin resistance in patients switching to raltegravir should be considered in future studies.

Maraviroc, while not explicitly studied in comparison with PI-based regimens, has not been shown to cause significant elevations of glucose in healthy volunteers, treatment naive subjects (in combinations with AZT/3TC in the MERIT study), or treatment-experienced subjects (in combination with optimized background therapy in the MOTIVATE trials) [65–67]. As such, maraviroc could be a glucose-neutral option for subjects with R5-tropic virus.

NRTI-sparing regimens—In the NONUKE trial, subjects with lipoat-rophy who switched from a NRTI-containing regimen to a NNRTI plus PI regimen experienced an improvement in mean 2-h oral glucose challenge values at week 48 that did not persist at week 96. No improvement in mean fasting glucose was noted at either time point [47].

Similarly, in ACTG A5152s, treatment-naive subjects were randomized to receive NRTIs plus efavirenz, NRTIs plus lopinavir/ ritonavir, or efavirenz plus lopinavir/ritonavir. Subjects in efavirenz-containing arms (with or without NRTIs) had statistically significant increases in median fasting blood glucose levels (efavirenz plus NRTIs = 4 mg/dl [5%], efavirenz plus lopinavir/ritonavir = 5 mg/dl [6%]; both $p < 0.05$); however, no changes in median fasting insulin levels or Quantitative Insulin Sensitivity Check Index values were observed [46]. In combination, these data suggest that a NRTI-sparing switch strategy may not be effective in improving ART-associated insulin resistance.

NNRTI-sparing regimens—Data on insulin resistance in subjects switching to NNRTI-sparing regimens are lacking. In a study of 563 treatment-naive subjects randomized to start FTC with either raltegravir or efa-virenz, subjects being administered raltegravir demonstrated minimal effect on mean fasting glucose [53]. While it is currently unclear whether switching to raltegravir could improve insulin-glucose homeostasis in a patient population with underlying dysregulation, it may be possible to extrapolate that switching a NNRTI to an agent shown to be relatively metabolically neutral (such as atazanavir, raltegravir and/or maraviroc) could result in stable if not improved markers of insulin resistance. Future studies are needed to confirm this hypothesis.

Multiple class-sparing regimens—As mentioned, Nozza *et al.* did not observe a change in glucose or insulin levels in triple-class experienced subject with R5-topic virus who switched from a failing regimen to a combination of maraviroc, raltegravir and etravirine [54]. Controlled clinical trials are needed to fully understand the potential benefit of NRTI-and PI-sparing regimens on insulin-glucose homeostasis.

Minimizing cardiovascular risk

HIV-infected patients both on and off ART are known to be at increased risk for CVD, and minimizing this risk is an important goal of long-term HIV management. Despite the potential effects of ART on parameters such as lipids and glucose, ART has been shown to improve markers of inflammation in HIV-infected subjects, and both the SMART study and ACTG A5102 suggested an increased cardiovascular risk in subjects undergoing periods of treatment interruption [9,11,68–70]. Whether individual antiretroviral agents contribute to cardiovascular risk independent of traditional risk factors remains controversial. In addition, multiple factors affect the assessment of cardiovascular risk in HIV-infected patients,

including: methods of quantifying risk (such as risk scores); time to and documentation of actual cardiovascular outcomes; use of markers of atherosclerosis such as carotid intima-media thickness (cIMT), arterial flow-mediated dilatation (FMD), and coronary calcium scores; physician preference for antiretroviral agents; patient risk factors (i.e., genetics, diet, and lifestyle factors such as smoking); and study type (observational or interventional). A summary of recent data on changes in surrogate measures of CVD and disease risk following a switch in ART is available in Table 3.

Switching within classes

Protease inhibitors—Endothelial dysfunction is a known precursor of CVD, and the formation of reactive oxygen species and mononuclear cell recruitment to a perturbed endothelium is a known contributor to the development of atherosclerosis. PIs have been postulated to induce these changes [71], which may contribute to the increased risk of CVD observed in HIV-infected persons. The PI indinavir has been directly implicated in endothelial dysfunction [72,73], but this does not appear to be a class effect of PIs.

In a study of healthy volunteers comparing unboosted atazanavir and lopinavir/ritonavir to placebo, no change in endothelial function was observed after 4 weeks of therapy with either PI [74], a finding that had previously been documented with lopinavir/ritonavir use [75]. In two studies of subjects with elevated LDLc who were suppressed on a PI-containing regimen, switch to unboosted or boosted atazanavir from any other PI did not improve brachial artery FMD, serum inflammatory markers, or markers of oxidative stress [21,23].

In the D:A:D study, cumulative exposure to both indinavir and lopinavir/ritonavir were associated with an increased risk of myocardial infarction after adjustment for traditional risk factors (relative risk [RR] per year 1.12 and 1.13, respectively) [14]. The French Hospital Database study found a similar increased risk of myocardial infarction with cumulative exposure to all PIs except saquinavir (OR: 1.15 per year; 95% CI: 1.06–1.26), with the strongest associations seen for amprenavir/fosamprenavir with or without ritonavir (OR 1.53 per year; 95% CI: 1.21–1.94) and lopinavir/ritonavir (OR 1.33 per year; 95% CI: 1.09–1.61) [76]. However, an ana lysis of the US Veteran's Affairs database did not show any association between ART use and cardiovascular events [77].

It remains unclear whether individual PIs contribute to CVD risk, and if so, what the magnitude of that risk is. Greater experience with darunavir is also needed in this setting.

Nucleoside reverse transcriptase inhibitors—The D:A:D study also observed an increased risk of myocardial infarction in subjects receiving aba-cavir or didanosine (RR for cumulative abacavir exposure = 1.07, RR for recent abacavir use 1.70, RR for recent didanosine use 1.41) [14]. The risk of myocardial infarction with NRTIs was primarily associated with recent exposure, compared with the association with cumulative exposure for PIs. By contrast, neither the French Hospital Database nor the Veteran's Affairs Database studies found a similar association with NRTI use and risk of myocardial infarction [76,77].

The SMART study reported elevated median hs-CRP and IL-6 levels, and an increased risk of CVD in subjects receiving abacavir (hazard ratio 1.91) [15]. However, other studies have not demonstrated this effect of abacavir or didano-sine, and subsequent attempts to implicate these agents as greater inducers of inflammation or endothelial dysfunction than other NRTIs has met with mixed results [78–81].

In the STEAL study, 357 subjects were randomized to switch their current NRTIs to FTC or abacavir/3TC. significantly fewer cardiovascular events were observed in the FTC arm (0.3 vs 2.2 events/100 patient-years; hazard ratio for tenofovir 0.12; p = 0.048) [35].

In the HEAT study, similar mean improvements in markers of endothelial activation and inflammation (vascular cell adhesion mol-ecule-1 [sVCAM-1], IL-6, and C-reactive protein) were seen in subjects initiating ART with either abacavir/3TC or FTC [82], suggesting that abacavir does not contribute to increased CVD via these mechanisms. However, in a study of 61 subjects receiving ART, subjects on abaca-vir had greater impairment in median brachial artery FMD (4.9 vs 2.8%; p = 0.01), a finding that could not be accounted for by adjusting for other risk factors or confounders [83].

In ACTG A5001, a long-term follow-up study of subjects originally randomized to different ART regimens in ACTG clinical trials, risk of CVD was associated with traditional risk factors, but not abacavir use, in 3205 subjects initiating ART [84].

Future, carefully controlled, prospective studies are needed to further elucidate the potential contribution of individual NRTIs to CVD risk in HIV-infected patients, and to evaluate the potential improvement in cardiovascular risk associated with switching antiretroviral agents. Given the low rates of cardiovascular events in studies to date, future studies will need to evaluate surrogate markers of subclinical atherosclerosis in order to better assess the short-term effects of ART switching on cardiovascular risk.

Non-nucleoside reverse transcriptase inhibitors—No NNRTI individual agent or class effect on risk of myocardial infarction was observed in the D:A:D, French Hospital database, or Veteran's Affairs database studies [13,14,24,76,77]. Longer-term data and prospective studies are needed to determine whether the NNRTI class of agents directly affects cardiovascular function.

Switching between classes

PI-sparing regimens—In the SHIVA study, ART use was correlated with risk of CVD as measured by mean cIMT and a composite cardiovascular risk scoring system. While PI use (particularly lopinavir) was statistically correlated with premature atherosclerosis, the authors concluded that this statistical association lacked clinical correlation, and that, based on available data, PI-sparing regimens should not be considered for this reason alone [85].

NRTI-sparing regimens—In a study of treatment naive subjects, Van Vonderen and colleagues compared subjects initiating AZT/3TC plus lopinavir/ritonavir to subjects initiating the NRTI-sparing regimen of lopinavir/ritonavir plus nevirapine. While not a switch study, similar mean improvements in markers of endothelial function (sVCAM-1, intercellular adhesion molecule [sICAM-1], von Willebrand factor antigen, plasminogen activator inhibitor-1 antigen, and C-reactive protein), and similar mean increases in cIMT and femoral artery stiffness were observed in both treatment arms [86], arguing against AZT and 3TC as contributors of excess CVD risk.

NNRTI-sparing regimens—In the MERIT study, use of maraviroc was associated with lower mean 10-year Framingham cardiovascular risk scores compared with efavirenz (week 24, 2.1 vs 3.0%; week 48, 2.2 vs 3.3%) [51]. As with other metabolic complications, recent data on NNRTI-sparing regimens is scant, but it is possible to hypothesize that switching to newer, more metabolically neutral agents could stabilize or improve these perturbations. Greater experience is needed with etravirine.

Multiple class-sparing regimens

Longitudinal data are needed to determine the contributions of newer antiretroviral agents, such as raltegravir and maraviroc, to CVD in the setting of HIV infection. These data would be useful both in treatment naive cohorts, in which subjects would not have potential contributions of past ART to CVD risk, and in switch studies, during which the reversibility or stabilization of CVD risk could be assessed in subjects who have increased risk due to prior antiretroviral use.

Conclusion

As long-term control of HIV infection becomes a reality for increasing numbers of patients, so does the need to optimize ART-associated comorbidities. While the selection of an antiretro viral regimen most likely to maintain virologic suppression remains the number one priority, switching ART to optimize common metabolic complications including lipid abnormalities, lipoatrophy and lipohypertro-phy, insulin resistance, and overall cardiovascular risk may be an effective strategy for some patients.

While the current literature is heterogeneous with regard to both study design and outcomes reporting, data exists supporting the benefits of switching to nonthymidine analog NRTIs, the PI atazanavir, and the HIV-1 integrase inhibitor raltegravir on some metabolic parameters (predominantly lipids and lipoatrophy). Whether the lipid benefits associated with ART changes will translate into a reduction in cardiovascular risk over the long term remains uncertain. At present, clinicians are left to individualize the management of patients and weigh risks and benefits in determining which antiretroviral agents are most likely to be favorable for a given patient. Continued assessment of both newer classes and nontraditional combinations of agents is needed to determine whether these agents and combinations could play a role in the prevention or reversal of long-term, ART-associated, metabolic complications.

Future perspective

As we learn more about the metabolic profiles of individual antiretroviral agents, new strategies for maintaining virologic control and minimizing metabolic complications will emerge. In addition, combinations of metabolically preferred antiretroviral agents and traditional therapies for disturbances such as lipid abnormalities and insulin resistance have the potential to provide improved outcomes over optimization of ART alone.

Standards and preferred methods both for preventing the onset of metabolic abnormalities and, once present, minimizing their severity have yet to be developed. Randomized, controlled studies of such strategies are needed to develop evidence-based treatment guidelines. However, the financial and time constraints associated with testing large numbers of ART combinations is prohibitive. Therefore, while carefully planned, randomized studies remain an important contribution, extrapolating trends from the growing body of literature on metabolic abnormalities will be necessary. Standardization of reporting methods for outcomes such as insulin resistance and cardio vascular risk will make this process easier, and should be attempted. In addition, maintaining virologic suppression after switching ART for specific metabolic complications must remain a priority, and correctly identifying the patients at lowest risk for virologic failure after switching ART will continue to be a challenge for the future.

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Table 1

Changes in lipids in subjects switching antiretroviral therapy

Investigators/ study (year)	Switch	Total cholesterol	Triglycerides	Low-density lipoprotein cholesterol	High-density lipoprotein cholesterol	Ref.
Stanley *et al.* (2009)	Lopinavir/ritonavir to atazanavir/ritonavir	−44.0 mg/dl (20%); p = 0.01	−155.0 mg/dl (51%); p = 0.02	NC	NC	[20]
SABAR (2010)	Other PI to atazanavir/ritonavir	−25.0 mg/dl (−12%); p = 0.009	−58.0 mg/dl (−23%); p = 0.013	NC	NR	[21]
AI424-067	Other PI to atazanavir	p < 0.0001[†]	p < 0.0001[†]	−24.0 mg/dl (−15%); p < 0.0001	p = 0.0007[†]	[22]
Flammer *et al.* (2009)[‡]	Other PI to atazanavir	−38.6 mg/dl (15%); p < 0.0001	−106.2 mg/dl (38%); p = 0.03	−27.0 mg/dl (18%); p < 0.0001	3.9 mg/dl (8%); p = 0.03	[23]
ARIES[¶] (2010)	Atazanavir/ritonavir to atazanavir	−13 mg/dl (−7%); p < 0.001	−40 mg/dl (−25%); p < 0.001	−8 mg/dl (−8%) p = 0.006	NC	[24]
SABAR (2010)	Other PI to atazanavir/ritonavir	−25.0 mg/dl (−12%); p = 0.009	−58.0 mg/dl (−23%); p = 0.013	NC	NR	[21]
SIROCCO (2007)	Efavirenz to nevirapine	NC	NC	−13.1 mg/dl; (−8%);p < 0.04	NC	[38]
STEAL (2009)	Other NRTIs to abacavir/lamivudine or tenofovir/emtricitabine	Abacavir vs tenofovir 15.4 vs −3.9 mg/dl (8 vs −2%); p < 0.001)	NC	NC	Abacavir vs tenofovir 0.0 vs −3.9 mg/dl (0% vs −8%); p = 0.004	[35]
SWITCHMRK (2010)	Lopinavir/ritonavir to raltegravir	−28.0 mg/dl (−13%); p < 0.0001	−84.4 mg/dl (−42%); p < 0.0001	NC	NC	[44]
SPIRAL[§] (2010)	Boosted PI to raltegravir	(−11%); p < 0.0001	(−22%) p < 0.0001	(−6%); p < 0.001	(−3%) p < 0.0001	[45]
NONUKE (2008)	NRTI to NNRTI + PI	NR	NC	3.1 mg/dl; (2%); p = 0.045	4.6 mg/dl (9%); p = 0.025	[47]
ACTG A5110[‡] (2009)	Thymidine analog to abacavir or NRTI to lopinavir/ ritonavir + nevirapine	Abacavir NC; lopinavir/ritonavir 24 mg/dl (12%) p < 0.001	Abacavir NC; lopinavir/ritonavir 56 mg/dl (21%)[#]	NR	Abacavir and lopinavir/ritonavir 3 mg/dl (9 and 10%); p = 0.05, p = 0.01	[48]

[†] Significant, but magnitude of change not reported.

[‡] Within-group p-value reported (otherwise, between-group p-value reported).

[¶] Percentage or absolute change calculated from available data.

§Absolute change not calculated secondary to available data.

#Within-group p-value not available.

NC: No (significant) change; NNRTI: Non-nucleoside reverse transcriptase inhibitor; NR: Not reported or not performed; NRTI: Nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor.

Table 2

Changes in fat in subjects switching antiretroviral therapy

Investigators/ study (year)	Switch	Visceral Adipose tissue	Subcutaneous adipose tissue (limb)	SAT (trunk)	Total fat	SAT:total fat	Ref.
Stanley et al. (2009)	Lopinavir/ritonavir to atazanavir/ritonavir	-25 cm^2 (22%); p = 0.047	NR	NR	NR	NR	[20]
SWEET (2009)	AZT/3TC to tenofovir/emtricitabine	NR	Within group change 0.26 kg (4%);p = 0.054 Between group change 0.45 kg; p = 0.025	NC	NC	NR	[30]
LIPOTEST[†] (2008)	Stavudine to tenofovir	NR	NR	NR	3.9 kg (21%); p < 0.001	NR	[33]
Madruga et al.[†] (2007)	Stavudine to tenofovir	NR	1.3 kg (29%); p < 0.0001	NR	NR		[31]
Milinkovic et al.[‡] (2007)	Stavudine to tenofovir	NR	0.4 kg; p = 0.0003	NR	NR	NR	[32]
ACTG A5110[†] (2010)	Thymidine analog to abacavir or NRTI to lopinavir/ritonavir + nevirapine	Abacavir -18.3 cm^2 (-15%); p = 0.04; lopinavir/ ritonavir NC	Abacavir 2.9 cm^2 (18%); Lopinavir/ritonavir 3.2 cm^2 (17%) Both p < 0.01 (thigh); no difference between switch arms	NR	NR	NR	[48]
NONUKE (2008)	NRTI to NNRTI + PI	NC	109 cm^3 (30%); = 0.001 (thigh)	NC	NR	0.07 (17%); p = 0.007	[48]
MONOI-ANRS 136 (2010)	Darunavir/ritonavir + NRTI to darunavir/ritonavir monotherapy	NR	0.34 kg (7%); p = 0.011	NC	NR	NR	[59]

Percentage or absolute change calculated from available data.

[†] Within-arm p-value reported (otherwise, between-arm p-value reported).

[‡] Percentage change not calculated secondary to available data.

3TC: Lamivudine;AZT: Zidovudine; NC: No (significant) change; NNRTI: Non-nucleoside reverse transcriptase inhibitor; NR: Not reported or not performed; NRTI: Nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor; SAT: Subcutaneous adipose tissue.

Table 3

Changes in measures of cardiovascular function in subjects switching antiretroviral therapy

Investigators/study (year)	Switch	Measurement	Result	Refs.
Flammer *et al.*[†](2009)	Other PI to unboosted atazanavir	FMD	NC	[23]
SABAR (2010)	Other PI to atazanavir/ritonavir	Cardiovascular inflammatory markers	NC	[21]
SIROCCO (2007)	Efavirenz to Nevirapine	FRS	−2% 10-year CVD risk	[38]
STEAL (2009)	Other NRTIs to abacavir/3TC or tenofovir/emtricitabine	Cardiovascular event rate	Tenofovir vs abacavir 0.3 vs 2.2 events/ 100 person-years; p = 0.048	[35]

[†]Within-arm p-value reported (otherwise, between-arm p-value reported).

3TC: Lamivudine; CVD: Cardiovascular disease; FMD: Flow-mediated dilatation; FRS: Framingham risk score; NC: No (significant) change; NRTI: Nucleoside reverse transcriptase inhibitor; PI: Protease inhibitor.