

RESEARCH INITIATIVE

Treatment Action!

Ten thoughts on how HIV care may change in 10 years By Mark Mascolini

Interviews with:

Charles W. Flexner, MD:

Mixed Forecast on the Future of Antiretroviral Therapy

Steven G. Deeks, MD:

One HIV Clinician's Toughest Challenges

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Dear reader,

It's been more than a quarter of a century since the dawn of the HIV epidemic, and though our losses have been staggering – more than 25 million have died from the virus worldwide since 1981 – so has the speed of our progress.

Today, we have almost two dozen medications, representing five classes, available for combating HIV. The most popular formulation allows for once-daily dosing with a single pill. Meanwhile, standard lab tests quantify with precision the amount of viral RNA in a patient's plasma, allowing clinicians to evaluate the efficacy of therapy and the risk of disease progression. Disease-free life expectancy for people with HIV – at least for those in the industrialized world – has soared. Today, Randy Shilts' mythic band would have reason to play on.

The rate and scope of advancement in HIV therapy are enough to make you wonder: What developments does the future hold? That's exactly the question our editor and his collaborators try to answer in this issue of *RITA!* They wonder, for example, about the prospects for using nanoparticles to produce once-a-month dosing, and how that could improve convenience, lessen side effects, and reduce drug resistance (p. 20). But they do more than wonder. The men and women editor Mark Mascolini has interviewed are among the very people who shape trends in HIV clinical practice and drive the agenda in HIV research. These are the clinicians and investigators who can tell you what's coming, and what isn't. They can tell you how the treatment of HIV in Europe may come to differ from the treatment of HIV in the United States. They can tell you, not insignificantly, how the epidemic might end (p. 27).

These aren't the sort of people who just wish things were different. These are the sort of people who make things different. Accordingly, their aspirations and predictions—and frustrations—merit our attention.

Until there's a cure,

A handwritten signature in red ink that reads "Paul".

Paul Simmons, RN, ACRN
Co-Executive Director/Programs

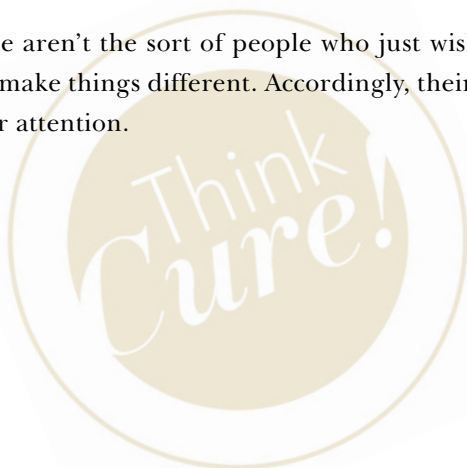


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Ten thoughts on how HIV care may change in 10 years

By Mark Mascolini

In the next 5 to 10 years, HIV physicians will routinely prescribe rescue regimens lacking nucleoside reverse transcriptase inhibitors (NRTIs). And they'll be boosting protease inhibitors (PIs) and perhaps other antiretrovirals with something besides ritonavir. But clinicians won't deploy immune-based therapies, they won't have once-a-month drugs, and they won't be trying to eradicate HIV from their patients.

Those prognoses come from a survey of 28 top clinical investigators and from an interview with leading HIV pharmacologist Charles Flexner (see page 38). This (unscientifically selected) panel of HIV seers (see page 7) gives even odds on two other treatment strategies that may emerge in the next several years: NRTI-sparing first-line and early-maintenance regimens, and treatment guided by genetic beacons (**Figure 1**). But most survey respondents see long odds against routine PI-boosted “monotherapy” for early maintenance, planned treatment interruptions for children, or nonantiretroviral strategies. One survey respondent, Huldrych Günthard from the University Hospital Zürich, suggests that treatment of acute or early HIV infection may play a regular role in the clinic—but only if more rigorous study confirms the value of that strategy.

Considering these same treatment tactics, our prognostic pros think some long shots for routine care nonetheless deserve urgent research attention, including PI maintenance monotherapy,

nanoparticle delivery of antiretrovirals, immune-based therapies, and especially eradication (**Figure 1**). But few panelists believe research dollars should flow to work on treatment interruptions in kids, and our experts are equivocal on whether pharmacogenetics or nonantiretroviral tactics merit more research.

This article analyzes research on the 10 HIV care modes considered by RITA's 28 treatment pundits, as well as their opinions of these strategies and published insights from other HIV savants. This issue also includes an interview with Charles Flexner (Johns Hopkins University School of Medicine) on these issues and an interview with Steven Deeks (University of California, San Francisco) on the prime challenges HIV docs face right now.

1. Renouncing nukes in early therapy

For the first 8 years of HIV treatment, NRTIs filled the top drawer—and the *only* drawer—of the antiretroviral medicine chest. Zidovudine, didanosine, zalcitabine, stavudine, and lamivudine all got the FDA green light before clinicians could craft a regimen with drugs from two classes.

NRTIs fell from favor as reports of long-term nuke toxicity accumulated. But approval of safer

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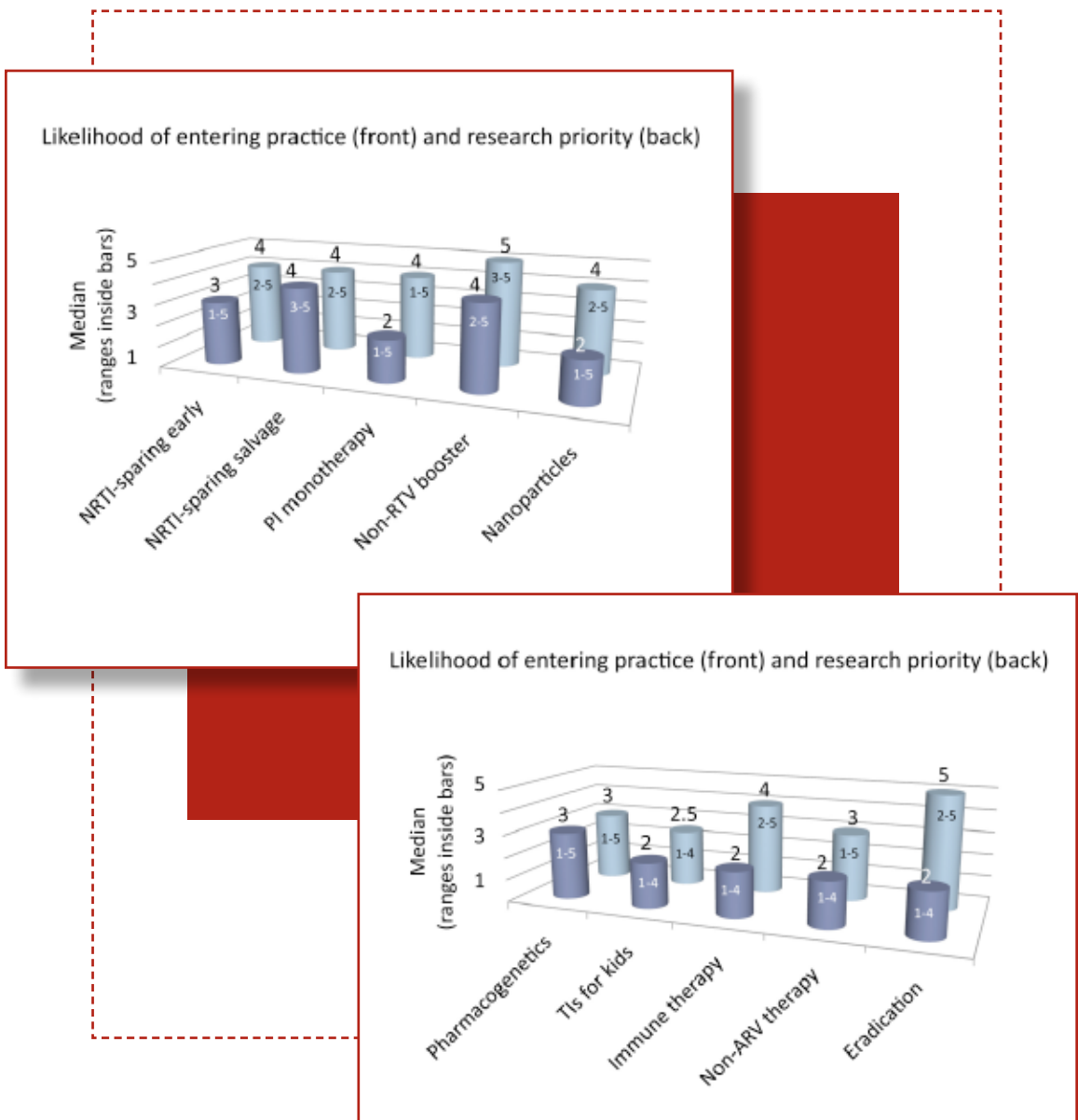


Figure 1. Twenty-eight clinical investigators answered a survey on 10 future options in HIV care. For each strategy, they rated its importance on the HIV research agenda, from a low of 1 (“not at all important”) to a high of 5 (“extremely important”), and its likelihood of entering routine practice in the next 5 to 10 years from a low of 1 (“not at all likely”) to a high of 5 (“extremely likely”). RTV, ritonavir; TIs, treatment interruptions; ARV, antiretroviral.

HIV Researchers Who Answered the Survey

Terrence Blaschke, MD, Stanford University School of Medicine, Stanford, California
Marta Boffito, MD, PhD, Chelsea and Westminster Hospital, London
Andrea De Luca, MD, Catholic University, Rome
François Clavel, MD, Hôpital Saint-Louis, Paris
Claudia Cortes, MD, Fundación Arriarán, Santiago, Chile
Eric Daar, MD, David Geffen School of Medicine at UCLA, Los Angeles
Steven Deeks, MD, University of California, San Francisco
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Federico Garcia, PhD, Hospital San Cecilio, Granada, Spain
Marshall Glesby, MD, PhD, Weill Cornell Medical College, New York
Huldrych Günthard, MD, University Hospital Zürich
W. David Hardy, MD, David Geffen School of Medicine at UCLA, Los Angeles
Keith Henry, MD, University of Minnesota, Minneapolis
Charles Hicks, MD, Duke University Medical Center, Durham, North Carolina
Andrew Hill, PhD, University of Liverpool
Akil Jackson, MB BS, Chelsea and Westminster Hospital, London
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Diego Ripamonti, MD, Ospedali Riuniti di Bergamo, Italy
Jürgen Rockstroh, MD, University of Bonn, Germany
Andrew Scourfield, MBBS BSc, Chelsea and Westminster Hospital, London
Davey Smith, MD, University of California, San Diego
Babafemi Taiwo, MBBS, Northwestern University Feinberg School of Medicine, Chicago
Laura Waters, MRCP, Chelsea and Westminster Hospital, London

RITA¹ invited 89 clinical investigators to answer a brief e-mail survey on the future of care for people with HIV infection in resource-rich countries. Twenty-eight (31%) responded in time for this article. No follow-up was sent to nonrespondents. Fourteen respondents (50%) work in Western Europe, 12 (43%) in the United States, and 1 each in Canada and South America.

yet still-potent NRTIs, and their coformulation in once-daily pills, may have rescued this class from impending oblivion. When the AIDS Clinical Trials Group (ACTG) tested an NRTI-sparing mix of lopinavir/ritonavir plus efavirenz against either of those drugs plus two NRTIs, they found the lowest 96-week incidence of lipoatrophy among people taking tenofovir, while twice as

many people eschewing nukes than taking them had to use lipid-lowering drugs.¹ The proportion of people with at least one new grade 3 or 4 lab abnormality was higher in the NRTI-sparing arm than in the other two arms, mainly because of high triglycerides ($P < 0.01$).²

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Despite the convenience and relative safety of once-daily fixed-dose tenofovir/emtricitabine and abacavir/lamivudine, both tenofovir and abacavir come with short- and long-term safety concerns. Tenofovir poses a threat to people with beleaguered kidneys,³ while abacavir is off-limits to people with a genetic risk of hypersensitivity⁴ and may ratchet up the risk of cardiovascular disease.^{5,6} As a result, the clinical trials engine has clanked into high gear to study nuke-shunning combinations for first-line or early maintenance therapy. Clinicaltrials.gov lists 15 trials (**Tables 1-4** in the interview with Charles Flexner) testing an array of no-nucleoside duos that join already-licensed antiretrovirals:

- Raltegravir plus atazanavir (with or without ritonavir)
- Raltegravir plus darunavir/ritonavir
- Raltegravir plus lopinavir/ritonavir
- Maraviroc plus darunavir/ritonavir (or atazanavir/ritonavir or lopinavir/ritonavir)
- Maraviroc plus lopinavir/ritonavir

In the interview in this issue of *RITA!*, Charles Flexner notes that the comely safety profile of raltegravir, and its low potential for interacting with other antiretrovirals, make it a good candidate for early NRTI-sparing medleys. But he thinks this strategy lost some allure with the advent of one-pill once-a-day triple therapy in Atripla, which may be followed by similar admixtures. Andrea De Luca (Catholic University, Rome) sees raltegravir/atazanavir as a strong NRTI-averting candidate, “but only for patients with Atripla toxicity.” And Huldrych Günthard cautions against undue early enthusiasm, recalling the fast demise of Trizivir as a first-line option.⁷ Günthard adds

that compartment penetration of NRTI-sparing combos awaits detailed study.

Overall, our 28-maven roster gave early no-nuke therapy a median score of 3 (on a scale of 1 to 5) in forecasting routine use of such combinations over the next 5 to 10 years. (On this scale, 1 means “not at all likely” and 5 means “extremely likely.”) These experts think NRTI-sparing early treatment deserves relatively high research interest, giving this tactic a median score of 4 on the 1-to-5 scale. (On this scale, 1 means “not at all important” and 5 means “extremely important.”) And indeed, ardent advocates of this approach already have early results for clinicians to mull.

Raltegravir with atazanavir claims an early lead in interest, perhaps because both drugs have good safety records. In Bergamo, Italy, Diego Ripamonti and colleagues are testing raltegravir/atazanavir (200/400 mg twice daily) in people switching from a PI or a nonnucleoside reverse transcriptase inhibitor (NNRTI) regimen with no major protease mutations, no raltegravir experience, and no proton pump inhibitor use.⁸ In this 27-person, noncomparative pilot study, all but 2 people (7%) had a viral load below 50 copies/mL 24 weeks after switching to two-drug therapy. Viral loads stood at 1421 and 107 copies/mL at the time of this report in the 2 people with detectable loads. No one stopped either drug or lowered the dose because of side effects or ominous lab values.

In a Los Angeles study, 2 of 30 people (7%) who switched to raltegravir/atazanavir after intolerance of a suppressive regimen had to stop the combination in 24 weeks, one because of side

2

effects and one because of virologic rebound.⁹ This noncomparative study tested atazanavir at a dose of 400 mg once daily and raltegravir at 400 mg twice daily in 30 people who maintained a viral load under 400 copies/mL for more than 4 months and had fewer than 50 copies/mL at screening. No one had tried raltegravir, no one had resistance to PIs, and no one had taken a failing PI regimen. The person with a virologic rebound was taking phenytoin, which lowers levels of some PIs. Elevated creatinine led one person to stop the combination. Seven people had HIV RNA blips ranging from 48 to 83 copies/mL through 24 weeks of follow-up.

Ultimately, Charles Flexner suggests, adoption of early NRTI-sparing therapy will depend on convincing results in a trial comparing such a regimen to a triple-therapy standard of care. He thinks the best two-drug candidate would be a coformulated once-daily combo, a pill still to be proposed. All the double-agent NRTI-sparing combos now under study rely on separate antiretrovirals, at least one of which requires twice-daily dosing.

2. Rescue regimens without one nucleoside

NRTIs-based rescue therapy has held sway since the first days of antiretroviral history: when zidovudine fails, try didanosine. Tacking on nucleosides gained some credence when combination antiretroviral therapy arrived, partly because evidence suggested even a partially active NRTI could add some oomph to salvage combos, and partly because mutant virus evoked by continuing NRTI pressure could be feebler than nonmutant virus or more susceptible to other NRTIs.^{10,11} But not all research backed that strategy.¹² And there are splendid reasons for banning marginally active NRTIs from any regimen: higher risks of side effects and drug interactions, and higher cost.

Recently, a provocative retrospective study from Montreal found an inverse correlation between number of salvage NRTIs and chances of virologic response through 24 weeks (**Figure 2**).¹³ Benoit Trottier and colleagues at Clinique Médicale l'Actuel studied 116 people who had

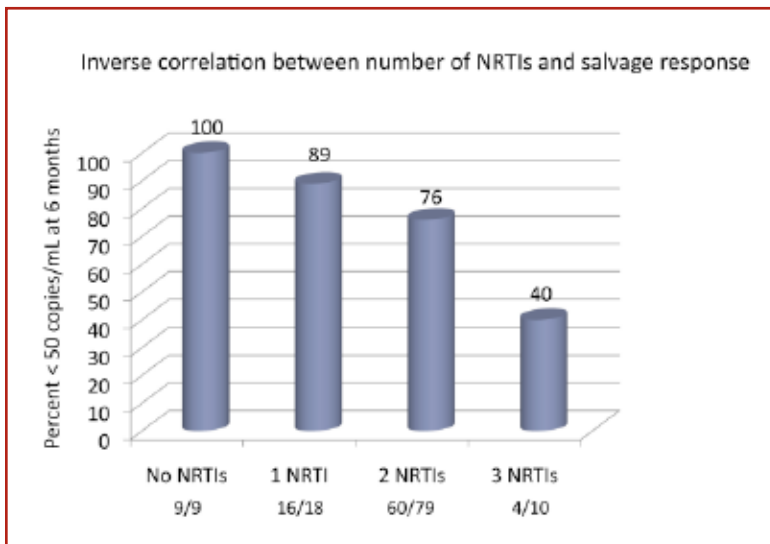


Figure 2. More NRTIs in a salvage regimen lowered 6-month sub-50-copy response rates in a retrospective Montreal study ($P = 0.009$). (Source: Benoit Trottier.¹³)

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taken antiretrovirals for a median of 13 years. Three quarters started a salvage medley containing four or more drugs. As in earlier studies, more *active* drugs in the regimen (judged by mutations in all available genotypes) correlated with a better chance of reaching a sub-50-copy viral load after 6 months ($P = 0.002$). But more *prescribed* antiretrovirals, including more prescribed NRTIs, did nothing to make virologic response more likely.

The dwindling chance of virologic response with each additional prescribed NRTI may well reflect physicians' perception that people with more resistant virus and fewer active antiretroviral options would benefit from extra nukes. So people in this clinic who took more NRTIs may have started salvage with a bigger risk of failure. But for many of them, piling on nukes didn't work.

The 28 clinical investigators who responded to our e-mail survey give NRTI-sparing salvage a median score of 4 out of a possible 5 in forecasting whether it will figure in routine practice over the next 5 or 10 years (**Figure 1**). They also give this strategy a median score of 4 out of 5 on the research priority scale.

The predicted demise of NRTI-laden rescue concoctions—a legacy of MegaHAART and GigaHAART days—can be traced partly to development of antiretrovirals in four classes with activity against resistant virus. “New drugs are so active that we should not need NRTIs if resistance has developed,” explains pharmacology expert Andrew Hill (University of Liverpool). Diego Ripamonti (Ospedali Riuniti di Bergamo) agrees that, these days, “most failing patients are on NRTI backbones with marginal effect, if any.”

Probably the most-pondered use of NRTIs to keep mutant virus in circulation involves sticking with lamivudine or emtricitabine to maintain M184V. A pilot study published in 2006 randomized people with M184V while taking antiretrovirals to stop all treatment or continue lamivudine alone at a once-daily dose of 300 mg.¹¹ After 48 weeks, 20 of 29 people (69%) in the treatment interruption group and 12 of 29 (41%) in the lamivudine group dropped out of the study because of clinical failure or because their CD4 count sunk under 350 cells/mm³, the study cutoff for immunologic failure. Although few clinicians would try either of these tactics today, the results hint that keeping M184V on the prowl pays immunologic dividends.

The COLATE trial, also published in 2006, took a different tack.¹² A lamivudine-containing combo was failing in all these patients, who then got randomized to continue or stop lamivudine while taking other antiretrovirals. After 48 weeks, viral load drops and CD4 gains did not differ between the 65 people on lamivudine and the 66 off lamivudine. Those findings suggest maintaining M184V has no virologic or immunologic value in people taking antiretrovirals.

An ongoing ACTG trial, OPTIONS, may settle the NRTI salvage questions, or at least offer some up-to-date insight.¹⁴ OPTIONS is still recruiting participants with triple-class antiretroviral experience or resistance while taking a failing PI regimen that includes two other antiretrovirals. The ACTG team splits enrollees into two groups: those who can build a new regimen with higher activity predicted by continuous phenotypic sensitivity score, and those whose new regimen has lower predicted activity. People starting a more

highly active regimen take three or four recent antiretrovirals (enfuvirtide, maraviroc, darunavir, tipranavir, etravirine, and/or raltegravir) with or without two or more NRTIs for 96 weeks. People starting a regimen with lower predicted activity all take two or more NRTIs for 96 weeks. The primary outcome is time to regimen failure. OPTIONS has enrolled nearly 600 people and should end in December 2011. Smaller ongoing trials could have results earlier.

3. Maintenance monotherapy with a boosted PI

In an interview starting on page 38, Charles Flexner calls maintenance PI monotherapy “one of the most interesting under-the-radar topics in antiretroviral therapy” that’s not “gotten the publicity it warrants.” As Flexner and RITA/ survey respondents note, solo boosted PIs to maintain an undetectable viral load have caught on in Europe, while US clinicians remain circumspect. Indeed, 14 Europe-based survey respondents gave PI monotherapy a median score of 4 (out of 5) when reckoning its likelihood of entering routine practice, while 11 US-based respondents gave the tactic of median score of 2. The overall median score (including one respondent in Canada and one in South America) was 2 (**Figure 1**). Still, the collective survey panel gives PI monotherapy a median score of 4 when weighing its merits as a research priority.

In the late 1990s, three randomized attempts to simplify treatment with a two-drug maintenance

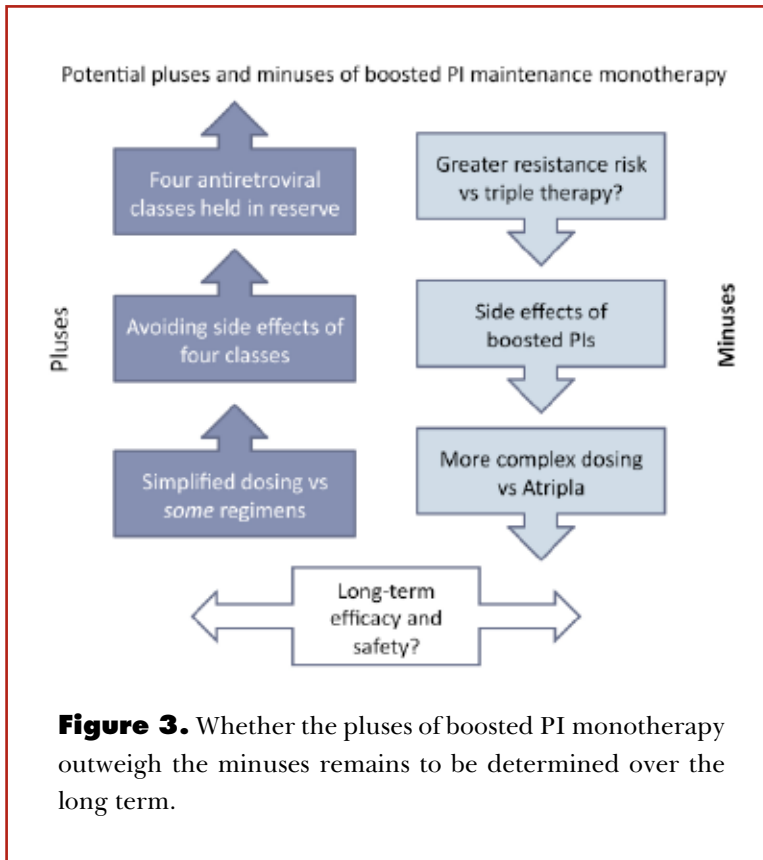
regimen foundered because the maintenance combos were feeble and had a low resistance threshold: nelfinavir/saquinavir, nelfinavir/stavudine, indinavir/zidovudine, zidovudine/lamivudine.¹⁵⁻¹⁷ The high barrier to resistance found with lopinavir/ritonavir and other boosted PIs in clinical trials, and the robust activity of boosted PIs, led clinical investigators to revive the induction-maintenance model with a boosted PI for maintenance.

Routine use of boosted PI monotherapy depends on the answers to three questions:

- Does PI monotherapy work as well as standard therapy?
- What’s gained with PI monotherapy?
- What’s lost with PI monotherapy?

The second and third questions are easier to answer. What’s lost with PI monotherapy is freedom from PI side effects and the greater convenience and simplicity of a one-pill once-a-day standard (Atripla) and possibly other multidrug fixed-dose combinations to come. What’s gained is keeping four antiretroviral classes in reserve: NRTIs, NNRTIs, entry inhibitors, and integrase inhibitors. Early on, convenience was a plus in PI monotherapy’s column, but not anymore. Now other first-line regimens include fewer pills that can be downed once daily, whereas lopinavir/ritonavir monotherapy is usually dosed twice daily, and darunavir/ritonavir was dosed once or twice daily in two early trials.^{18,19} Whether a boosted PI might cause fewer long-term side effects than a three-drug regimen remains to be seen.

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To answer the first question, Wouter Bierman and Dutch colleagues took a hard look at ritonavir-boosted monotherapy in a systematic review of 22 trials presented through May 2008.²⁰ This analysis does not embrace MONET¹⁸ and MONOI,¹⁹ the 256- and 242-person trials of darunavir/ritonavir maintenance monotherapy. Nor does it include a recent 60-person Swiss HIV Cohort Study trial that stopped early because of a higher failure rate with lopinavir/ritonavir monotherapy than with triple therapy.²¹ Slicing the available data in nearly every direction imaginable, Bierman usually found a virologic advantage with continued standard therapy versus monotherapy.

Pooling the six randomized controlled trials, which all involved lopinavir/ritonavir, Bierman figured nearly a 50% higher risk of virologic failure with monotherapy than with continued triple therapy (odds ratio [OR] 1.48, 95% confidence interval [CI] 1.02 to 2.13, $P = 0.037$) by intention-to-treat analysis. Among 364 people randomized to lopinavir/ritonavir monotherapy, 121 (33.2%) met virologic failure criteria, compared with 64 of 280 people (22.9%) maintaining standard therapy. In an as-treated analysis, the risk of failure proved more than 3 times higher with monotherapy (OR 3.56, 95% CI 2.00 to 6.32, $P < 0.001$). As-treated data showed 72 failures among 315 people (22.9%) who switched to monother-

apy versus 17 failures among 233 people (7.3%) who stayed with standard therapy.

Virologic response to lopinavir/ritonavir monotherapy did approach the response to standard therapy (77% versus 82%) in the four randomized trials that included people who had an undetectable viral load for at least 6 months on standard therapy and were usually taking lopinavir/ritonavir as part of that therapy. In these four trials, monotherapy failed in 40 of 177 people (22.6%), while 31 of 176 people on standard therapy (17.6%) met failure criteria, a nonsignificant difference ($P = 0.24$).

If people who lost viral control on monotherapy regained control when resuming standard therapy are not counted as failures, the failure rate did not differ significantly between monotherapy and standard therapy in an intention-to-treat analysis. But Bierman and coworkers believe “the validity of this [last] analysis is limited due to incomplete data and unclear or lacking protocol definitions of intensification.” Thus, they argue, “there is yet insufficient evidence and follow-up to regard this intensification strategy as safe.” And in an as-treated analysis with regained viral control no longer counted as failure, monotherapy carried more than a doubled risk of failure (OR 2.15, 95% CI 1.17 to 3.92, $P = 0.013$). In the lopinavir trials, major PI resistance mutations arose in 10 of 61 tested people whose monotherapy failed (16%) versus 1 of 12 (8%) whose standard therapy failed.

Of the two darunavir/ritonavir monotherapy trials presented to date, the French MONOI trial¹⁹ looks less convincing than the European MONET trial¹⁸ for three reasons: (1) darunavir/ritonavir monotherapy was “not noninferior” to darunavir/ritonavir triple therapy in one of two 48-week

MONOI analyses, (2) 3 people randomized to monotherapy and none randomized to maintain triple therapy had a virologic failure in MONOI, and (3) the failure threshold in MONOI was 400 copies/mL, rather than the 50 copies/mL in MONET.

MONET involved 256 Europeans with a viral load below 50 copies/mL for at least 6 months on standard therapy.¹⁸ No one had tried darunavir, and no one had a record of virologic failure. The 127 people randomized to monotherapy took darunavir/ritonavir in a dose of 800/100 mg once daily, while 128 people in the control arm switched to once-daily darunavir/ritonavir plus two NRTIs.

Defining virologic failure as consecutive viral loads above 50 copies/mL, the MONET team calculated 48-week response rates of 86.2% with monotherapy and 87.8% with triple therapy in a per-protocol analysis counting drug switches as failures and excluding 10 people with protocol violations. An intention-to-treat analysis that included the 10 protocol violators found nearly identical 48-week response rates with monotherapy (84.3%) and triple therapy (85.3%). An analysis that allowed drug switching also found similar response rates. In all three analyses, monotherapy was not inferior to triple therapy. Successful postfailure genotypes of 22 people on monotherapy and 13 on triple therapy found one primary PI mutation and one darunavir mutation in a person on monotherapy and M184V plus one primary PI mutation in one person on triple therapy.

Does darunavir penetrate critical compartments like the central nervous system (CNS) and geni-

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tal fluids? So far, research suggests adequate CNS penetration. A study of 18 people taking standard darunavir-based therapy in California determined that cerebrospinal fluid concentrations of darunavir exceeded the median inhibitory concentration for wild-type virus (2.75 ng/mL) in all 18 people by a median 20.7 fold.²² In MON-ET neuropsychiatric side effects were infrequent with darunavir/ritonavir as monotherapy or with two nucleosides.²³ Most reported side effects were grade 1 and not drug related. Cognitive function scores did not differ between the monotherapy group and the triple-therapy group.

The ongoing PIVOT trial may offer further insight into the pluses and minuses of darunavir/ritonavir monotherapy.²⁴ Although PIVOT physicians are allowed to use any ritonavir-boosted PI, trial guidance recommends lopinavir/ritonavir or darunavir/ritonavir and it appears that most physicians are prescribing darunavir/ritonavir.²⁵ PIVOT aims to randomize 400 people in the UK and Ireland to monotherapy or triple therapy and to track virologic failure and resistance rates for 5 years. Three trials of lopinavir/ritonavir monotherapy for people coinfecting with HIV and HCV are underway.²⁶⁻²⁸

Two clinical investigators who responded to our survey, Davey Smith (University of California, San Diego) and Huldrych Günthard, hope research can uncover a marker of response to PI monotherapy, but neither favors trying monotherapy in practice now. One study did suggest that a low nadir CD4 count predicts failure of lopinavir/ritonavir monotherapy.²¹ That randomized trial ended early with an unexpectedly high failure rate in the monotherapy arm.

Two European researchers, Marta Boffito (Chelsea and Westminster Hospital, London) and Andrea De Luca, give monotherapy the highest mark, 5, when predicting its routine use in the next decade. But US researchers evinced markedly less enthusiasm. “Since the ritonavir and the second PI are often the most inconvenient and/or toxic parts of a regimen,” Steven Deeks observes, “it is unclear why this approach (which has risks) would be preferred over standard approaches.” David Hardy (David Geffen School of Medicine at UCLA, Los Angeles) seconds that opinion: “With the availability of two dual NRTI fixed-dose combinations with minimal short-term toxicity,” he argues, “the rationale [for PI monotherapy] remains unjustifiable.” Both Deeks and Hardy scored maintenance monotherapy 1 on the 1-to-5 scale forecasting regular clinical use.

4. Boosting with something besides ritonavir



Most HIV researchers who responded to RITA's survey think clinicians will be boosting PIs—and maybe other antiretrovirals—with something besides ritonavir in the next several years. Our panel gives non-ritonavir boosting a median score of 4 (out of 5) in presaging prospects for adding such a drug to daily practice (**Figure 1**). The median research priority score for such agents is 5.

Because ritonavir potently inhibits the enzyme that all currently favored PIs depend on for their metabolism (CYP 3A4), modern antiretroviral therapy would look very different without this drug. The investigational integrase inhibitor elvitegravir also relies on CYP 3A4 to attain

adequate concentrations. But ritonavir has disadvantages. Even low boosting doses may cause side effects, especially over the long term; the ritonavir capsule requires refrigeration; and ritonavir is not coformulated with any antiretroviral but lopinavir.

Drug developers have unveiled three new boosters in human trials, GS-9350 from Gilead Sciences,²⁹ SPI-452 from Sequoia Pharmaceuticals,³⁰ and PF-03716539 from GSK-Pfizer.³¹ Of the three, GS-9350 has the biggest lead in clinical research with two phase 2 trials underway. One trial compares Atripla with GS-9350, elvitegravir, tenofovir, and emtricitabine—melded into a single once-daily tablet tentatively called QUAD—in previously untreated adults.³² The primary endpoint of this 75-person trial is the proportion of people with a viral load under 50 copies/mL at week 24, and Gilead expects to have that result by the end of 2009. Because GS-9350 has no anti-HIV activity, its use in low doses without a PI, as in this trial, should not select PI-resistant virus.

Another phase 2 trial compares a single 150-mg tablet of GS-9350 with a 100-mg ritonavir capsule, both combined with 300 mg of atazanavir and standard-dose tenofovir/emtricitabine, all once daily, in antiretroviral-naïve adults.³³ Primary endpoint data (proportion with a 24-week viral load under 50 copies/mL) should be collected by January 2010. Because of its solid dosage form, GS-9350 may be amenable to coformulation with atazanavir or other non-Gilead antiretrovirals.

In an online interview, Gilead's Brian Kearney suggests other potential advantages of GS-9350 over ritonavir: (1) more specific inhibition of CYP 3A enzymes versus CYP 2C and CYP 2D6 enzymes, (2) lack of CYP 3A induction, which could

limit unwanted interactions, and (3) reduced impact on adipose sites, which may translate into a benign lipid profile.³⁴ Kearney adds that, besides teaming with Bristol-Myers Squibb on combining GS-9350 and atazanavir, Gilead is “engaging in conversations with other companies to conduct pharmacokinetic studies to see if our drugs can work together.”

Despite clinical fervor for a new booster, our survey respondents caution that only long-term use can establish the value and safety of new PK kickers. “Proving that this approach is without long-term complications will require years and years of careful observation,” says Steven Deeks. “Hence, even if non-ritonavir boosting is benign, it will be many years before this is a settled issue.” Charles Flexner tenders a similar proviso in the interview in this issue of *RITA!*

And in the meantime, HIV docs may find their reliance on boosting agents ebbing. “The need to use hepatic enzyme inhibition as a major strategy will probably decline over time,” David Hardy forecasts, “as more potent, unboosted options become available.”

5. Treatment interruptions for children

5

SMART³⁵ (on top of more than a few other studies) killed structured treatment interruptions, right? But what about giving kids treatment breaks? Does anyone really expect a child infected at birth and starting antiretrovirals swiftly to keep on taking them for 50, 60, or 70 years? Yes, several researchers who answered our survey say.

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Suspending therapy for children is “a really bad idea,” insists Carl Fichtenbaum (University of Cincinnati). Diego Ripamonti thinks drug holidays for kids “are good only if we lack drugs.” Other panelists proved equally cautionary, with the whole group giving this tactic a median score of 2 (on a 1-to-5 scale) in sizing up prospects for routine clinical use (**Figure 1**). As a research priority, respondents score pediatric treatment interruptions with a lukewarm 2.5. Alone among surveyed experts who offered comments, Joel Gallant (Johns Hopkins University, Baltimore) suggests drug breaks are “potentially attractive to get kids through their adolescence,” but he says he’s “not optimistic that it will be safe.”

RITA’s e-mail brain trust for this article includes no pediatricians (though some were invited), and at least a few leading HIV pediatricians think structured treatment breaks merit close scrutiny for their patients. Indeed, two large international trials of drugs layoffs in children—PENTA 11 and BANA 2—were recruiting when the avalanche of bleak data put this tactic off-limits for adults, but the pediatric planners decided not to fold their trial tents.

Are pediatricians being obtuse, or merely obstinate? A review article by HIV pediatricians Hannah Green and Diana Gibb of Britain’s Medical Research Council suggests obstinacy in this case may rest on good reason.³⁶ Even the safest antiretrovirals pose a threat of long-term toxicity, and that toxicity “has increased potential to adversely affect children” who are growing rapidly while taking antiretrovirals. The threat of bone toxicity is particularly vexing in children, Green and Gibb write. They argue that “for biological as

well as social reasons . . . the role of treatment interruptions in children may differ from adults.”

The biological reasons include different responses to antiretroviral therapy because of a still-developing but energetic immune system, a higher viral load during infancy, and “differences in pharmacokinetic handling of drugs that vary with age across childhood.”³⁶ The social reasons center on adherence, which is an entirely different issue in children than in adults because childhood adherence depends largely on the care giver. Poor adherence is more likely to engender cross-resistance to one antiretroviral class after another in children who start treatment early and face decades of adherence hurdles.

Structured treatment interruption has not been thoroughly studied in children. The only interruption study listed in ClinicalTrials.gov that exclusively recruited children stopped before it started³⁷ because similar trials in adults showed that on-and-off therapy did little to stimulate the immune system into fighting HIV. A study of 4 children with antiretroviral-controlled chronic infection found that cycles of 4 weeks off treatment and 12 weeks on lowered viral rebound points with each interruption.³⁸ A similar strategy in a large trial of chronically infected adults (cycles of 2 weeks off and 8 weeks on) perked up HIV-specific cellular immunity but failed to improve viral control.^{39,40}

Results of what appears to be the first completed randomized trial of planned drug breaks in children were presented at the 2006 International AIDS Conference⁴¹ but not published. Children randomized to the interruption arm in this

30-child study stopped antiretrovirals (zidovudine, lamivudine, and abacavir) when their viral load became undetectable and restarted after a 10-fold rebound. Twenty-seven children completed 48 weeks of follow-up, but only 9 in the interruption arm became eligible for a drug break. There were no serious adverse events, no new AIDS diagnoses, and no deaths in either arm.

Three ongoing randomized treatment hiatus trials in children use CD4% or CD4 count to guide drug breaks. PENTA 11 focuses on 100 children from 2 to 15 years old with well-controlled viremia while taking a stable regimen.⁴² The PENTA team randomized them to continuous therapy or CD4-guided breaks (stop until CD4% falls below 20% in 2- to 6-year-olds; stop until CD4% falls below 20% or CD4 count falls below 350 cells/mm³ in older children; stop if interruption lasts 48 weeks). The primary endpoints are number of children in each arm with (1) a CD4% below 15% for 2- to 6-year-olds or a CD4% below 15% or a CD4 count under 200 cells/mm³ for older children, (2) a new CDC stage C diagnosis, or (3) death.

After a median 130 weeks of follow-up, no child died or had a new stage C event.⁴³ There were 4 primary endpoints in the interruption group and 1 in the control group, a nonsignificant difference ($P = 0.2$). Mean change in CD4 count from weeks 0 to 72 was 134 cells/mm³ lower in the interruption group ($P = 0.01$), but 6 children in the interruption arm were off therapy at the week-72 check-up. CD4 recovery after treatment interruption was significantly better in younger children. At the 72-week point, 85% of children in the continuous-therapy arm and 58% in the in-

terruption group had a viral load below 50 copies/mL ($P = 0.003$), but (again) 6 children in the interruption arm were off treatment at week 72. Among 13 children with consecutive viral loads above 100 copies/mL, 10 (5 in each arm) had new resistance mutations. Annual follow-up of all children in PENTA 11 will continue for 5 years.

The ongoing CHER trial randomized vertically children to four arms: (1) defer antiretroviral therapy until necessary if CD4% is at least 25%, (2) receive antiretroviral therapy until first birthday if CD4% is at least 25%, (3) receive antiretroviral therapy until second birthday if CD4% is at least 25%, or (4) receive continuous antiretroviral therapy if CD4% is less than 25%.⁴⁴ Compared with children who deferred therapy, those who began immediately had a 76% lower death rate and a 75% lower progression rate.⁴⁵ The study is continuing among immediately-treated children to compare stopping after the first or second birthday.

BANA II, the largest pediatric HIV trial in Africa, randomized 600 Botswana children who took a PI regimen for at least 6 months to continue therapy or to suspend treatment based on CD4 count.³⁶ Toxicity is the primary endpoint, though BANA II will also compare costs of the two strategies. Recruitment ended in July 2008.

Although CHER and BANA II probably cannot by themselves determine whether structured treatment interruptions will work better—and be safer—in children than in adults, they may at least help HIV pediatricians decide whether to pursue study of this strategy.

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6. Using genes to steer antiretroviral therapy



No medical prospect beguiles journalists or beleaguers Orwellians more than the possibility that our very genes may become Big Brotherly busybodies that betray our physiologic failings or fortitudes. What cancers may lurk, what infections may threaten, what cures may fail will one day all be read in our garrulous DNA.

Perhaps.

Although science has tracked down a herd of genetic disease determinants, their clinical use (or abuse) remains largely unrealized. One celebrated exception comes from the arena of HIV medicine—the discovery that the MHC class I allele *HLA-B*5701* marks people susceptible to abacavir hypersensitivity reaction.^{46,47} A thoughtfully planned and conducted randomized trial helped usher *HLA-B*5701* screening into clinical practice.⁴ And British experts Tabitha Mahungu, David Back, and colleagues “remain hopeful that a similar discovery [of a prospective genetic test for hypersensitivity] awaits nevirapine.”⁴⁸

Yet, as Steven Deeks observes in replying to RITA’s survey, “the uptake of *B*5701* testing has been slow and incomplete,” even though “it’s unlikely there will ever be a more powerful pharmacogenetic tool in HIV infection (or perhaps in all of medicine).” That anomaly, he continues, “suggests there will be many barriers to clinical use of any future markers.”

Other survey respondents fear pharmacogenetics may prove too expensive (Andrew Hill, Davey Smith), inaccurate (Andrew Hill), or complicated

(Carl Fichtenbaum) to work in HIV medicine. Overall, researchers who answered our survey gave pharmacogenetics a median rank of 3 (on a scale of 1 to 5) when presaging the possibility of routine clinical use in the next decade (Figure 1). They also gave pharmacogenetics a median score of 3 when reckoning research priorities.

Nonetheless, the flood of HIV pharmacogenetic research already impresses. A Pubmed search of “pharmacogenetics AND HIV” returned 169 articles, while “pharmacogenomics AND HIV” dug up 196. Huldrych Günthard tells RITA! the Swiss HIV Cohort Study has “very strong” (though still unpublished) data on the strength of genetic markers in HIV pharmacology. The study cataloged 14 genetic markers on 10 genes, including *HLA-B*5701*, cytochrome P450 markers for efavirenz, and uridine diphosphate-glucuronosyl transferase markers for atazanavir.

HIV medicine already has its own pharmacogenetics Website (www.hiv-pharmacogenomics.org) that lets users probe a database by gene, metabolizing enzyme, drug transporter, toxicity type, or treatment response.

Gene reading holds promise far beyond pinpointing predisposal to antiretroviral side effects. Amalio Telenti, a pharmacogenetic visionary at the University of Lausanne, thinks genetic signals may also help predict HIV disease progression and virologic response.⁴⁹ Speaking at the 5th IAS Conference in July 2009, Telenti made these points:

- We can now explain up to 22% of population differences in viral load on the basis of common variants, demographics, and population factors.
- At the individual level, these types of data may translate into prediction of disease progression.

Single-nucleotide polymorphisms (SNPs)—or “snips” in our DNA fabric—help ordain the disposition, toxicity, and possibly efficacy of NRTIs, NNRTIs, and PIs.⁵⁰ Telenti cited numerous studies correlating genetic glyphs with antiretroviral levels and suggested such findings may aid dose adjustments to prevent toxicities.⁴⁹ Examples already pondered (**Figure 4**) include nevirapine hypersensitivity and hepatotoxicity; efavirenz plasma levels and central nervous system side effects; atazanavir-linked hyperbilirubinemia; NRTI-related pancreatitis; tenofovir-associated renal proximal tubulopathy; and antiretroviral-associated peripheral neuropathy, lipodystrophy, and hyperlipidemia.

Elizabeth Phillips and Simon Mallal (Murdoch University, Perth), who pioneered the *HLA-B*5701* research, caution that much work remains before other genetic determinants find their way into the clinician’s office: Despite discovery of many markers related to pharmaco-

netics, efficacy, and toxicity of antiretrovirals, they write, “most of these have not been reproduced by more than one group.”⁵¹ And “although many such associations have furthered our knowledge of the pathophysiology of specific diseases, few will have clinical application.”

In e-mail to *RITA!*, Elizabeth Phillips suggests pharmacogenetics may become a valuable tool to identify new drug targets and to select drugs in early development “that are more likely to be associated with broad efficacy and few significant toxicities.”

But as far as clinical use goes, Charles Flexner strikes an admonitory note in an interview with *RITA!*, saying he has “not seen very many examples of genetic determinants of outcomes for antiretrovirals that are strong enough to suggest to me a high likelihood that it will change the way we prescribe those drugs.”

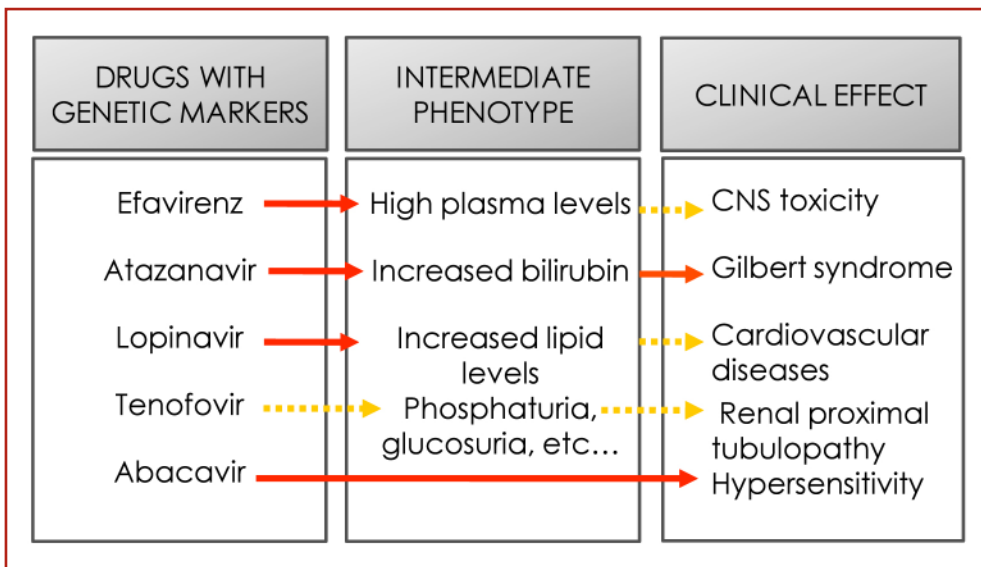


Figure 4. Already identified genetic markers could help pick out patients prone to several familiar antiretroviral side effects. (Illustration courtesy of Amalio Telenti.⁴⁹)

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If gene wrinkles other than *B*5701* do find their way into practice, Phillips and Mallal suggest their use could be more complicated than screening for abacavir hypersensitivity.⁵¹ “Ultimately,” they write, “for some drugs, drug levels may be needed to validate or supplement genetic information. This type of algorithmic approach would appear to be necessary for many other antiretroviral drugs, such as efavirenz, where the drug-metabolizing genotype can be complex and is only one piece of information ultimately factoring into the drug dose.”

Filling in the boxes of such algorithms would take more time and money than screening for a single gene. One way to save money, Mahungu and Back suggest, could be a “move away from single candidate gene analyses towards a high throughput whole genome approach.”⁴⁸ But refining and validating such an approach will not be easy.

Amalio Telenti remains confident that genetics can play a clinical role. He believes what’s being asked of pharmacogenetics is rarely asked “from many ‘support’ tests in the clinic: very high sensitivity, specificity, and positive or negative predictive value.” And funding to establish the clinical value of gene screening remains hard to come by, he adds. “When I present a prospective grant, the reviewers ask me for retrospective data, and when I try to publish the retrospective data, the reviewers say that it has no value, as only prospective data is to be believed.”

7. Nanoparticles to cut dosing and sharpen targeting

Nanotechnology could transform therapeutics for HIV infection and countless other condi-

tions. No clinician needs convincing that dosing a drug once a month instead of once or twice a day would make life easier for patient and clinician alike. Because nanoparticles have to be injected, presumably in the clinic, adherence would be easy to track. HIV pharmacologist Diego Ripamonti thinks nanoparticle-toted antiretroviral therapy is the ideal “first choice—if it works.”

Broadly speaking, a nanoparticle measures 100 nm or less (one ten-thousandth of a millimeter), though many antiretroviral nanoparticle studies involve bigger spheres.⁵² Squeezing HIV molecules into pipsqueak polymer particles that release the drug slowly after injection could make once-monthly dosing possible.⁵³ But the promise of nanogirth antiretrovirals goes far beyond infrequent dosing. Nanoparticle advocates Thirumala Govender and colleagues at Durban’s University of KwaZulu-Natal believe nanoparticle delivery and sustained release of antiretrovirals “may allow for their improved efficacy, decreased drug resistance, a reduction in dosage, a decrease in systemic toxicity and side effects, and an improvement in patient compliance.”⁵²

As if this weren’t enough, tweaking the nanoparticle surface may make it possible to target hard-to-reach infected cells, like brain macrophages (**Figure 5**).⁵⁴ Some work suggests that silver nanoparticles home to HIV’s gp120 spikes, which the virus uses to snare CD4 cells.⁵⁵

Antiretroviral nanotechnology is nothing new. It dates back at least to the dawn of HAART, when German researchers offered results on nanoparticle porters of saquinavir and zalcitabine.⁵⁶ Since then, other scientists have loaded nanoparticles with zidovudine,⁵⁷⁻⁶¹ didanosine,^{62,63} stavudine,⁶⁴ lamivudine,⁵⁷ delavirdine,⁶⁴ efavirenz,⁶⁵⁻⁶⁷ indinavir,^{68,69} ritonavir,^{67,70} and lopinavir.⁶⁷ But the nano-sized antiretroviral that most intrigues nanomas-

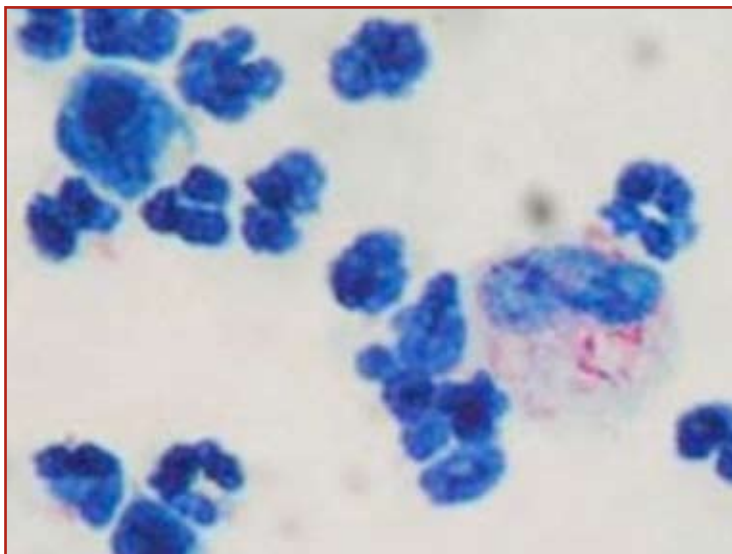


Figure 5. Besides promising dosing as infrequent as monthly, nanoparticle delivery of antiretrovirals may also help target hard-to-reach cells like macrophages. (Image courtesy of AIDS Images Library www.aidsimages.ch.)

ters today is Tibotec's investigational NNRTI, rilpivirine (TMC278), which has reached early-stage trials in humans.

The standard oral formulation of rilpivirine has already piqued interest because of its high oral bioavailability, long half-life, and knack for stalling HIV in previously untreated people⁷¹ and people in whom NNRTIs have already failed.⁷²

At the 2008 Conference on Retroviruses, Tibotec investigators unveiled results of nanoparticle delivery to rats, dogs, and humans.⁷³ Rilpivirine-packed nanoparticles trickled out measurable drug levels for 2 months in dogs and up to 6 months in humans. Although subcutaneous injections lasted longer than intramuscular shots in rats and dogs, subcutaneous delivery had no advantage in human volunteers, who often had injection site reactions to subcutaneous shots.

Modeling suggested that a once-monthly 600-mg injection of nanosuspended rilpivirine may achieve trough levels similar to 25 mg of oral rilpivirine daily.

Most RITA/ survey respondents don't expect to be injecting their patients with nanoparticles during the next decade. They gave antiretroviral nanotherapy a median grade of 2 (on a scale of 1 to 5) when predicting routine use over the next 5 to 10 years (**Figure 1**). But these clinical investigators generally concur that nanoparticle research deserves high priority, with a median rating of 4.

Pharmacologist Charles la Porte (University of Ottawa) foresees "lots of work before this gets to the clinic." Joel Gallant believes "the challenge will be to come up with entire regimens that can be dosed infrequently, as a single agent won't be

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enough.” Indeed, at the 15th Conference on Retroviruses, Tibotec’s Gerben van’t Klooster said the company is looking for other antiretrovirals it can mix with rilpivirine in the same nanoshots.⁷³

8. Prospects for immune-based therapy

In the early 1990s, reporters covering the Conference on Retroviruses often stopped first at the Immune-Based Therapy Workshop, where HIV immunologists divulged details of their latest research on stalling HIV not by attacking the virus, but by jiggering immune cells. That meeting disappeared years ago. aidsmeds.com, which offers steady updates on licensed and unlicensed antiretrovirals, last revamped its immune-based therapy page on June 28, 2006.

Are these signals that HIV experts have given up on immune-based therapy? Not entirely. Plenty of research continues, but certainly not at the pitch of the late 80s and early 90s. Reasons for this decrescendo are clear. When Clifford Lane and colleagues at the National Institute of Allergy and Infectious Diseases started testing interleukin 2 (IL-2) in people with AIDS,⁷⁴ there *were* no antiretrovirals. Physicians and people with HIV were keen to try anything that seemed to slow the ineluctable descent to AIDS. And IL-2 certainly pumped up CD4 counts. After antiretrovirals arrived, a randomized trial comparing antiretrovirals alone with antiretrovirals plus IL-2 found an average CD4 gain from 428 to 916 cells/mm³ in the IL-2 group after 1 year, and an average drop from 406 to 349 cells/mm³ in the control group.⁷⁵

But the question that dogged IL-2 research from day 1 was whether the CD4 cells you add with IL-2 fight off AIDS. After 7 years of study and outlays of over \$100 million, the answer was no. The 6000-person ESPRIT and SILCAAT trials reached essentially the same conclusions:⁷⁶ People taking IL-2 plus antiretrovirals gained significantly more CD4 cells early in treatment than those taking antiretrovirals alone. But the extra T cells did not lower the risk of disease progression or death, and serious side effects plagued significantly more people taking IL-2. ESPRIT and SILCAAT investigators had to conclude that, in the age of potent antiretroviral combinations, IL-2 doesn’t help, and it may hurt.

The protracted and expensive demise of IL-2 in ESPRIT and SILCAAT did not put an end to research on immune-modifying therapies—or even to research on IL-2—in people with HIV. In a study begun before reports of ESPRIT and SILCAAT results, IL-2 alone in people not taking antiretrovirals because their CD4 count exceeded 300 cells/mm³ seemed to delay progression.⁷⁷ Significantly fewer people in the IL-2 group than in the no-treatment group reached a primary endpoint (CD4 count below 300 cells/mm³, AIDS, or death): 35% versus 59% ($P = 0.008$). People taking IL-2 got by without antiretrovirals for an average of 92 more weeks than people in the control arm.

But the data and safety monitoring board recommended stopping IL-2 therapy after lymphoma developed in 3 people taking this agent versus 1 in the control arm. In an editorial analyzing the trial, Daniel Kuritzkes (Harvard University) observed that the primary endpoint difference mainly reflects higher CD4 counts in the IL-2 group, “a difference that the ESPRIT and SILCAAT studies show does not translate into clinical benefit over the longer term.”⁷⁸

If IL-2 can't help people with HIV, how about IL-7? Research suggests IL-7 can do lots of good things for HIV-infected people. It boosts levels of naive and central memory T cells.⁷⁹ It enhances cytotoxic T-lymphocyte function.⁸⁰ And, perhaps most importantly, it rouses latent HIV in people taking antiretrovirals.⁸¹ But so far IL-7 has yielded no clinical benefit in people with HIV.

A 40-person placebo-controlled trial of three doses of recombinant human IL-7 (r-hIL-7) found that the median CD4 count rose from 268 to 419 cells/mm³ after 12 weeks in people taking 10 μg and from 240 to 563 cells/mm³ in people taking 20 μg, both significant improvements (*P* = 0.006 and *P* = 0.004).⁸² CD8 counts also rose in both groups. Results with a 30-μg dose were not available at the time of this presentation. Everyone in the trial had taken a suppressive antiretroviral regimen for at least 1 year. No one taking r-hIL-7 dropped out of the trial, and no one had clinical

or laboratory side effects higher than grade 2. Neutralizing anti-IL-7 antibodies did not become detectable during the study. The trial confirmed earlier reports of CD4 gains with IL-7.^{80,83}

When asked if IL-7 advocates will need 7 years and millions of dollars to figure whether r-hIL-7 has any clinical value, Yves Levy argued that r-hIL-7 cannot be compared with IL-2 because it produces CD4 cells of an entirely different phenotype. Although he did not detail a comprehensive trial strategy, Levy suggested the next step will be to test several cycles of r-hIL-7, instead of the single cycle tested in this trial, to see if longer treatment sustains T-cell gains.

Other immune-transmuting strategies have come and gone—or seek revival in a different guise (**Figure 6**). Added to antiretroviral therapy, the immune modulator Remune sparked production of HIV-specific T cells but failed to prolong

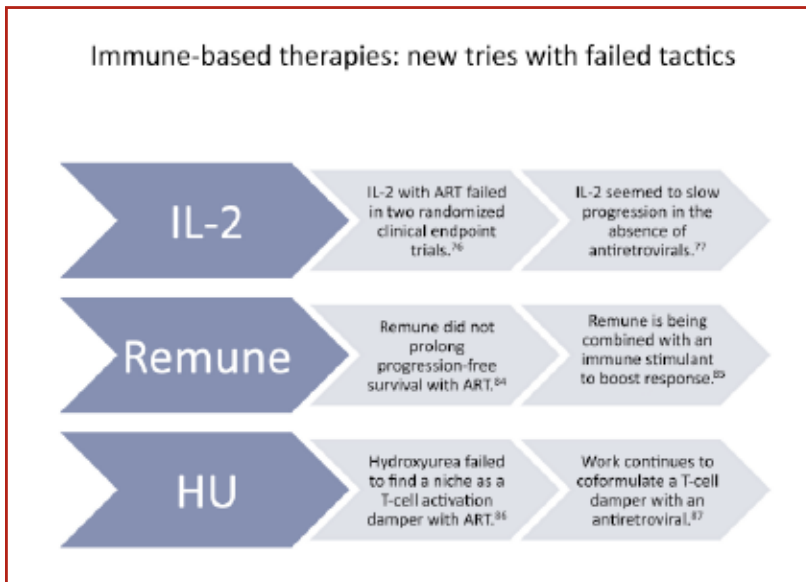


Figure 6. Despite numerous setbacks in randomized trials of immune-based therapies, researchers continue to pursue immune strategies that will enhance clinical responses to antiretroviral therapy (ART).

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HIV progression-free survival in a randomized trial.⁸⁴ At last notice, the developer was working on a new agent combining Remune and an immune stimulant meant to perk up responses to Remune.⁸⁵ For several years, researchers studied hydroxyurea to limit T-cell activation while treating people with standard antiretrovirals.⁸⁶ Ultimately, this cytostatic drug offered too little to offset its toxicity. Hydroxyurea champion Franco Lori is now trying to develop a “virostatic” (antiviral cytostatic) agent that combines a cytostatic other than hydroxyurea with an antiretroviral.⁸⁷ Two weeks of cyclosporin A produced no sustained immunologic response in a randomized trial that enrolled people starting antiretrovirals with chronic HIV.⁸⁸

A 48-week double-blind, placebo-controlled trial in antiretroviral-treated people showed that daily recombinant human growth hormone provoked HIV-specific CD4- and CD8-cell responses.⁸⁹ And work continues on “therapeutic vaccines” that might help the immune system rein in HIV.⁹⁰

Clinical investigators who responded to RITA’s survey believe work on immune-based strategies should continue, giving this field a median score of 4 (on a scale of 1 to 5) when weighing research priorities (Figure 1). But most survey respondents don’t expect an immune-tinkering tool to see clinical use soon (median score of 2 on a scale of 1 to 5). Huldrych Günthard seems to sum up the overall panel response, saying pilot studies of immune therapies “are always important, but I do not expect too much out of them.”

David Hardy is more optimistic, proposing that immune-based therapies may prove particularly valuable in an aging HIV population. “Despite

the lack of clinical benefit in the long-term IL-2 studies,” he writes, “IL-7 and other immunomodulators appear highly promising for future clinical research studies. If continued positive results are seen, direct application to clinical practice, especially in patients facing immunosenescence, is easy to imagine.”

9. Weighing merits of other nonantiretroviral strategies

Even if immune-based therapies fail to find a niche in daily HIV care, can agents other than antiretrovirals help infected people enough to play a role in clinical practice? Responding to RITA’s survey, pharmacologist Andrew Hill, not known as a micronutrient guru, suggested vitamin D may prove important in HIV management. Other possibilities include compound nutritional supplements, such as NR100157, which aimed to improve gut integrity and nutritional status in a recently completed randomized trial.⁹¹

A team of top HIV gastroenterologists and virologists concocted this intestinal tonic, which includes oligosaccharides (simple sugars that promote healthy gut bacteria and suppress harmful bacteria while decreasing systemic CD4 activation), n3-PUFAs (polyunsaturated fatty acids that decrease inflammation and gut permeability), bovine colostrum (nutrient-rich milk that enhances gut integrity), N-acetyl cysteine (an amino acid that improves glutathione status), and a vitamin/mineral mix (to prevent micronutrient deficiencies).

The BITE trial randomized 340 adults naive to antiretrovirals to NR100157 or a control substance.⁹¹ NR100157 is a powder that can be dissolved in liquid or mixed in food. Study participants from Argentina, Australia, Brazil, Italy, the

Netherlands, Thailand, the UK, and the United States had an average CD4 count in the low 400s and viral loads averaging 30,000 to 35,000 copies/mL. The data and safety monitoring board recommended stopping BITE early because the NR100157 group gained significantly more CD4 cells through 52 weeks than the placebo group (68 versus 28 cells/mm³ in an intention-to-treat analysis, $P = 0.030$). At that point only 60 people had completed the treatment course with NR100157, compared with 83 taking placebo.

At a conference session where Argentina's Pedro Cahn detailed these findings, Harvard's Daniel Kuritzkes claimed to be "stunned" that the review panel would advise halting the trial—and that the investigators would agree—when the statistical difference between the two study arms had reached only 0.03. In responding to *RITA's* survey, Joel Gallant agrees that BITE "was far from definitive, and it sounded like the supplement was more poorly tolerated than most ART regimens." (Thirty people gave up on NR100157 because of potential adverse reactions, compared with 14 who stopped placebo because of perceived side effects.) But Gallant suggests NR100157 "could have some relevance, especially in developing countries." David Hardy also thinks BITE stopped too soon, "but if positive results can be established," he predicts "acceptance in clinical practice will be great."

Because NR100157 targets the immune cell-rich intestinal wall, it could be considered an immune-based intervention of sorts. So could vitamin D, which regulates bone metabolism (a critical issue for a population at risk of osteoporosis), fortifies skeletal muscle,⁹² and has numerous possible immune-modulating properties. This essential micronutrient comes from solar synthesis and diet as 25(OH)D, and experts consider circulating 25(OH)D the best indicator of vitamin D status.⁹³

The vitamin abounds in fish liver oils, egg yolks, and fortified dairy products.

None of that would mean much if research didn't suggest HIV-infected people are prone to vitamin D deficiency, but plenty of research does.⁹⁴⁻¹⁰⁰ For example, a study of 57 adult US outpatients in the winter and spring of 2005 found that 37% had moderate 25(OH)D deficiency (10 to 20 ng/mL) and 10.5% had severe deficiency (10 ng/mL or less).⁹⁴ Low vitamin D intake correlated significantly with severe deficiency ($P = 0.01$), and people with lactose intolerance tended to have severe deficiency ($P = 0.08$). A Dutch study of 252 people with HIV found that 29% had vitamin D deficiency and that dark skin independently predicted low D levels. Study participants taking NNRTIs had a significantly lower median 25(OH)D3 level than those taking PIs (54.5 versus 77.3 nmol/L, $P = 0.007$).

A cross-sectional study of 1077 HIV-infected outpatients at a London clinic from June to December of 2008 found vitamin D deficiency in 73.5% and severe deficiency in 35%.⁹⁶ In 845 people taking antiretrovirals, the study tagged four factors that independently predicted vitamin D deficiency: black race (odds ratio 2.6, $P < 0.001$), measuring vitamin D in winter (odds ratio 2.1, $P < 0.001$), nadir CD4 count below 200 cells/mm³ (odds ratio 1.4, $P < 0.05$), and current efavirenz therapy (odds ratio, 1.9, $P < 0.001$). Another study produced evidence that PIs impair vitamin D activation to its active form, 1,25(OH)2D.⁹⁷

In a comprehensive review of vitamin D in people with HIV, Eduardo Villamor from the Harvard School of Public Health observes that studies like these are limited by lack of an HIV-negative control group and by their cross-sectional design.⁹³ But a few studies do have control groups

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or follow-up. A German comparison of 65 men with HIV, 35 women with HIV, 20 men without HIV, and 20 women without HIV measured significantly lower levels of 1,25(OH)₂D (the active form of vitamin D) in the HIV groups.⁹⁸ A later study by the same researchers that expanded the female sample to 50 women with HIV and 50 control women recorded significantly lower concentrations of 1,25(OH)₂D and 25(OH)D in the women with HIV.⁹⁹ None of these women were taking antiretrovirals. An Italian study that measured 1,25(OH)₂D levels at two points separated by 14 months tracked a drop in 27 people taking antiretrovirals.¹⁰⁰ Levels of 1,25(OH)₂D were significantly lower in 172 HIV-infected people, 20 of them with no antiretroviral experience, than in 64 people without HIV.

Low D levels may do more than threaten bones in people with HIV. Multivariate analysis in a study of 884 Tanzanian women with HIV determined that women with vitamin D levels below 32 ng/mL were 50% more likely to transmit HIV to newborns through the first 6 weeks after delivery and twice as likely to pass the virus to breast-feeding children not infected at 6 weeks.¹⁰¹ Children born to D-deficient mother had a 61% higher risk of dying during follow-up.

A small longitudinal Norwegian study found that 9 HIV-infected people with 1,25(OH)₂D concentrations under 25 pg/mL when the study began had a significantly shorter survival than 44 people with normal levels in an analysis that adjusted for CD4 count ($P < 0.01$).¹⁰² The study also measured lower 1,25(OH)₂D in 31 people with symptomatic HIV infection (median 34 pg/mL)

than in 22 asymptomatic people with HIV (median 45 pg/mL) or in 28 HIV-negative controls (49 pg/mL).

One study even suggested that certain vitamin D receptor gene sequences may lower the risk of HIV acquisition.¹⁰³ This analysis of 335 injecting drug users (IDUs) with HIV, 125 IDUs without HIV, and 124 healthy controls without HIV determined that five vitamin D receptor haplotypes cut the risk of HIV infection 60% ($P = 0.0025$).¹⁰³

What do these diverse findings mean for HIV medicine today? Villamor concludes that vitamin D deficiency is not “a likely cause of decreased 1,25(OH)₂D in the course of HIV infection, since low concentrations of 25(OH)D have been found in some but not all the studies.”⁹³ But he cautions that the limitations of these studies “preclude the exclusion of vitamin D deficiency as a potentially serious problem among HIV-infected individuals, particularly in populations with limited exposure to sunlight for cultural or geographical reasons.”

Villamor thinks the correlation between poor vitamin D status and mortality in one small study¹⁰² should be confirmed, “for example, by measuring metabolites of vitamin D in stored samples from patients who have participated in longitudinal HIV studies.”⁹³ ClinicalTrials.gov lists several ongoing trials of vitamin D supplementation in adults and children with HIV. While awaiting these and other findings, it may prove prudent to test HIV-infected people for vitamin D deficiency and to work toward correcting low levels.

10. Eradication: an elusive goal worth pursuing?

A protective HIV vaccine and eradication of HIV from infected people remain the twin grails of HIV research, and both remain beyond the reach of early 21st century science. But of the two, eradication seems more feasible. Indeed, some believe HIV has already been scoured from all cell sites and sanctuaries of at least one person.

Explaining “where HIV lives” in 2004, almost a decade after early enthusiasm for eradication wilted, Justin Stebbing, Brian Gazzard, and Daniel Douek proposed that eliminating HIV from infected people is “eminently achievable.”¹⁰⁴ Fifteen years later, Douglas Richman and other HIV virtuosi tried to rally support for more eradication research, writing that “a drug-free remission should be the new goal of HIV therapeutics.”¹⁰⁵ Although none of the 26 researchers who responded to our survey thinks eradication will be possible in the next 5 or 10 years, 20 of them (77%) gave it the highest research priority ranking, and 5 of the remaining 6 awarded it the second-highest ranking (**Figure 1**). Eradication and finding a nonritonavir booster were the only research priorities that attained a median score of 5 (the highest priority). But the median score for clinical application of eradication in 5 to 10 years languished at 2 and ranged from 1 to 3.

The goal of eradication research “is the optimal outcome” of HIV medicine, explains David Hardy. “But it carries with it the highest risk for failure due to our incomplete understanding of how the combined forces of human immunity, antiretrovirals and immune modulators may be able to interact to accomplish this goal.”

As Charles Flexner observes in his interview with *RITA!*, eradication may be possible, but only at an unacceptable risk to the patient. Joep Lange, who tested an eradication tactic in the 1990s,¹⁰⁶ put the problem in a nutshell at the 2009 IAS Conference: “The question is whether, with advances in HIV therapy, striving for HIV eradication in more than a few specific cases, is worth the drastic interventions likely to be required to accomplish this.”¹⁰⁷

HIV researchers caught the eradication bug as soon as they learned that triple antiretroviral combinations swiftly flush HIV from the circulation. Would a steady clamp on HIV replication eventually bleed viral reservoirs dry? Working with David Ho, Alan Perelson famously predicted that only 2 to 3 years of “completely inhibitory treatment would be required to eliminate HIV-1 from these [actively and latently infected cell] compartments.”¹⁰⁸ But Ho and Perelson also warned that “even longer treatment may be needed” to mop up HIV completely “because of the possible existence of undetected viral compartments or sanctuary sites.” And it didn’t take long for Robert Siliciano and others to show that the stubborn mound of latently infected CD4 cells melted at a glacial rate in the face of robust regimens.¹⁰⁹

A few years later, though, eradication enthusiasts found what they believed was the first patient who had HIV one day, then—after a suspended course of hydroxyurea, didanosine, and indinavir—did not. It seemed that this now-unortho-

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dox regimen, started soon after infection, kept HIV from springing back during a treatment break taken against his physician's advice, though smatterings of virus lurked in lymph nodes.¹¹⁰ It turned out that the Berlin patient carried an *HLA B*57* allele linked to long-term nonprogression, so whether this man's treatment and subsequent drug break played a role in his tight viral control remains unknown.¹¹¹

Another HIV-infected Berliner also managed to evade viral rebounds for more than a year without treatment. But it wasn't easy. Four years of efavirenz, tenofovir, and emtricitabine kept HIV in check and boosted CD4s to 415 cells/mm³ in this 42-year-old man.¹¹² But he had to stop his regimen because of renal failure following a first course of chemotherapy for newly diagnosed acute myeloid leukemia. When he resumed antiretroviral therapy, plasma viremia again became undetectable, but relapse of the leukemia led his physicians to undertake allogeneic stem-cell transplantation.

Knowing that the *CCR5 delta32* allele protects against infection with CCR5-using virus, these physicians sagely sought a stem cell donor homozygous for that *recherché* gene. Later, after whole-body irradiation, this man had a second transplant from the same donor, which led to complete remission of the leukemia. It also led to complete control of HIV replication without antiretrovirals, for 20 months.

Rectal biopsy 159 days after the second transplant turned up CCR5-expressing macrophages, which indicated that the transplant had not helped this man rebuild a completely HIV-resistant immune system. "These long-lasting cells from the host can

represent viral reservoirs even after transplantation," the physician warn, but "HIV-1 DNA could not be detected in this patient's rectal mucosa."¹¹² Nor could RNA or proviral DNA assays find HIV in peripheral blood or bone marrow.

This is a very lucky man. Not only did he manage to fight off acute myeloid leukemia, he also managed to keep HIV under wraps for 2 years without antiretroviral therapy. But is he cured—as a flurry of lay media reports claimed? It depends on what you mean by cure. If you mean keeping HIV out of circulation without antiretrovirals, he's cured, for now. But if you go by Jean-Pierre Routy's definition of cure, he's probably not. Routy, who plumbs viral reservoirs at Montreal's McGill University, thinks cure means three things: (1) no evidence of disease or symptoms, (2) eliminating every functional virion, and (3) eliminating every infected cell.¹¹³

More to the point, the withering therapy endured by the second Berlin patient is not something most people responding to antiretrovirals would countenance. And something no clinician would prescribe to anyone but a patient who needs a bone marrow transplant to save his life. As many as one third of patients who have such transplants die, according to the Berlin surgeons.¹¹⁴ On top of that, finding matched *CCR5 delta32* donors for many people with HIV would be impossible. The Berlin patient's physicians tested 61 candidate donors before they found one with *delta32* who agreed to share stem cells.¹¹⁵

Eradicating HIV means not only evicting every last viable virus from resting CD4 cells, it probably also mean rooting HIV from every cell of monocyte/macrophage lineage in anatomic hide-

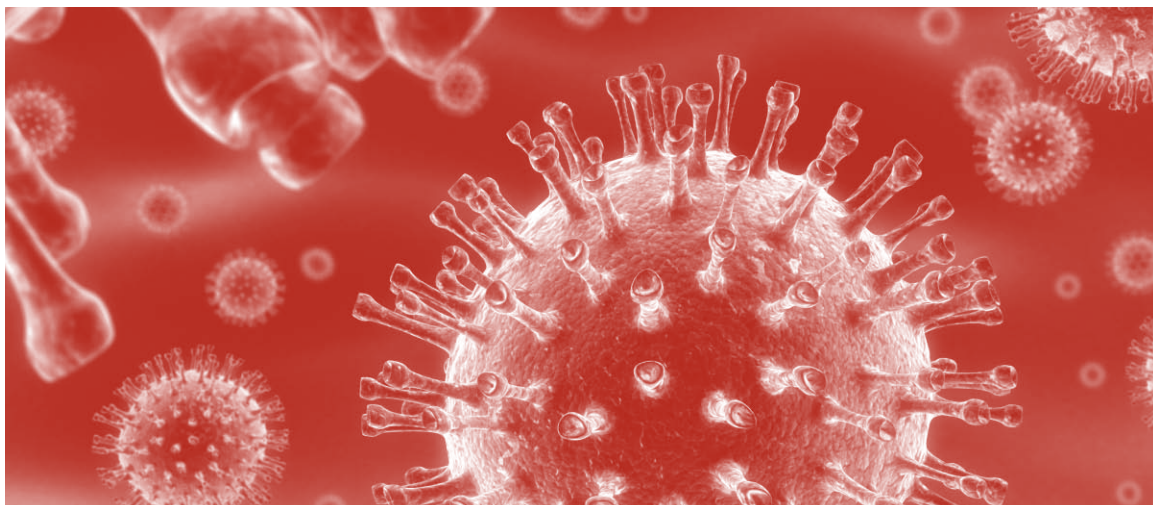
outs like the brain, gut, and lymph nodes. But that hasn't stopped scientists from pursuing an eradication strategy with a code name worthy of US military derring-do: shock and kill. Routy credits Dean Hamer of the National Cancer Institute with devising—or at least naming—this strategy.¹¹⁶ The idea, tried as early as 1999 by Lange and colleagues,¹⁰⁶ is to flood the body with an *agent provocateur* that perks up slumbering virus and so exposes it to standard antiretrovirals. And there is no shortage of candidates for this job.

Lange and coworkers tried IL-2 and OKT3, a monoclonal antibody that homes to the CD3 molecule.¹⁰⁶ But that combo proved too toxic, and it promptly spawned antibodies against OKT3. Other candidates include IL-7 and kinase agonists such as prostratin.¹⁰⁵ Today the preferred contenders are histone deacetylase (HDAC) inhibitors.^{117,118} But finding a latent cell “shocker” from one of these classes may not expose all virus even in the resting cell stash, Richman and coauthors caution, because discovering other latency

mechanisms would mean “entirely new classes of therapeutic agents able to safely alter host RNA expression or transport will be required.”¹⁰⁵

Responding to *RITA!*'s survey, Steven Deeks called the obstacles to eradication “daunting,” but because “curing HIV seems to be as likely or more likely than developing an effective vaccine,” it “should be a key focus of future research.”

Richman and colleagues argue that antiretroviral interruption trials after viral activation and elimination “are required if we wish to cure HIV.”¹⁰⁵ But they counsel that, “although the potential benefit to humanity is great, the benefit to the early trial volunteers is nearly nonexistent.” These experts say shock-and-kill will work only if industry backs the effort with “high-throughput drug candidate screening; medicinal chemistry; product synthesis, production, and formulation; toxicology; and pharmacology.” But whether industry will want to spend lots of time and money curing a money-making disease is another question.



Finding and treating recent HIV infection

Answering RITA's survey, Zürich's Huldrych Günthard suggests treating primary or early HIV infection may pay dividends rich enough to merit wide application. People diagnosed and treated early "may be the ones who can better profit from simplified maintenance treatment," Günthard argues, because they have a high CD4 count, limited viral diversity, and perhaps a still-inchoate latent reservoir. But he thinks research on this strategy remains spotty.

Most people with primary HIV infection escape diagnosis, perhaps partly because they get through it with only modest symptoms and partly because many physicians called on to care for primary infection syndrome never order an HIV test. French PRIMO cohort investigators estimate that people diagnosed with primary HIV infection represent only 5% of all new diagnoses in France and only 8% of all new infection.¹ Still, even with their diagnostic radar feebly tuned to HIV, French clinicians diagnosed 325 primary infections yearly between 1992 and 2002. And if research showed distinct rewards for treating early infection, diagnostic antennae would prick up.

A case-control study of people who started antiretrovirals within 6 months of infection found that 15 of 17 had undetectable cell-associated infectivity 1 year after treatment began, whereas none of 17 controls starting treatment during chronic infection achieved that goal.² French researchers showed treating primary HIV infection induced CD127 expression on CD8 cells comparable to that of nonprogressors.³ CD127 expression correlated positively with CD4 count and proliferative capacity of CD8 cells, and CD8 cells did proliferate avidly with treatment.

But another French team found that starting antiretrovirals before or after HIV seroconversion had little impact on HIV-specific CD4 or CD8 responses.⁴ These investigators also found that HIV-specific proliferative responses burgeoned in the first 18

months of infection in people with detectable viremia whether they were treated or not. A study of the French PRIMO and SEROCO cohorts recorded no long-term CD4 benefit in 170 people who started antiretrovirals within 3 months of infection—then suspended therapy—compared with 123 people who did not begin treatment.⁵ Another study of these same cohorts found that starting antiretrovirals early did not lower the viral set point.⁶

Improving understanding of early HIV pathogenesis, and strategies aimed at countering HIV's rapid devastation of immune defenses, could yield more consistently salutary results. But until then, the rationale for early treatment remains tenuous.

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Mixed Forecast on the Future of Antiretroviral Therapy

An interview with **Charles W. Flexner, MD**

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Nucleoside-sparing first-line regimens

Mascolini: There's a fair amount of ongoing work testing nucleoside reverse transcriptase inhibitor (NRTI)-sparing first-line regimens, either protease inhibitors (PIs) with raltegravir or PIs with maraviroc (**Tables 1-4**). So far, are these combinations looking OK pharmacokinetically?

Flexner: Yes. One of the attractive things about combining the integrase inhibitor raltegravir with other antiretrovirals is its low potential for drug-drug interactions. That, combined with its very good safety profile and activity results to date, makes it one of the more attractive antiretrovirals for this kind of application.

Having said that, I think combination regimens are becoming more convenient in general as a consequence of coformulation, so the entire concept of an NRTI-sparing regimen doesn't have nearly the urgency it did maybe 5 years ago, when we were more worried about convenience and toxicity.

I think you can draw a distinction between the attractiveness of such a regimen for treatment-naive

versus treatment-experienced patients. Certainly most treatment-naive patients can tolerate a co-formulated drug like Atripla (efavirenz/tenofovir/emtricitabine). We don't worry very much about the toxicities of lamivudine and emtricitabine any more except in patients who are chronically coinfecting with hepatitis B virus. And the only patients in whom we have a concern about tenofovir toxicity are patients with underlying kidney disease or people at risk of developing renal insufficiency.

Mascolini: Given those facts, do you think there's enough enthusiasm to push these no-NRTI combinations through trials into clinical practice for previously untreated people?

Flexner: If we could develop a two-drug, co-formulated, once-a-day combination that lacked a nucleoside analog and show in a large, prospective, randomized clinical trial that it is as good as the current gold standard—which right now is Atripla—I think clinicians would be very attracted to that. But a lot would depend on pricing and other issues. I do think it is possible to put together two very potent antiretrovirals with good safety profiles and produce a regimen that at least in a treatment-naive population would be seen as more attractive than Atripla.

NRTI-sparing options for experienced patients

Mascolini: The ACTG OPTIONS trial¹ and other trials are exploring NRTI-sparing salvage therapy. What are the potential pluses and minuses of this approach?

Flexner: The biggest minus of a nucleoside-sparing regimen in a heavily treatment-experienced patient population is that we don't yet have much experience with head-to-head comparisons of an NRTI-sparing regimen and an NRTI-containing regimen. Also, we are comfortable with the value and activity of NRTI-containing regimens even in patients who are highly treatment experienced. So for example I think we've come to believe—whether it's true or not²⁻⁴—that using lamivudine or emtricitabine in a regimen to maintain the M184V mutation is probably of some virologic benefit. But I could make the case that the virologic benefit of maintaining that M184V so far has been quantitatively modest. I could certainly see that in a head-to-head comparison it might not make that much difference.

The real issue is whether we're capable of doing comparative effectiveness research that will provide enough evidence to change the practice of medicine. In other words, will a trial like the OPTIONS trial provide definitive evidence that an NRTI-sparing regimen is better than or equivalent to the current practice, which in most cases is to include NRTIs in the regimen? And the answer to that question will await the outcome of the study.

Maintaining early response with PI monotherapy

Mascolini: We've seen lots of work on maintenance therapy with lopinavir/ritonavir alone,⁵

and recently with darunavir/ritonavir.^{6,7} Are the potential benefits of this approach worth the potential risks?

Flexner: This is one of the most interesting under-the-radar topics in antiretroviral therapy. I don't think it's gotten the publicity it warrants. Boosted-PI monotherapy is becoming *de facto* a very popular strategy in Europe for treatment-naïve patients. Why this is appealing to the European docs and not to the US docs, I don't know. Part of it may be drug pricing and who's paying for drugs and the benefit to the government payer of using one drug versus three. But part of it may also be that most of the simplification research has been done in Europe, and they feel this is their idea and they ought to be using it.

In a patient who is fully suppressed, I think there's a strong virologic rationale to use a simplification strategy that involves a potent boosted protease inhibitor with a high genetic barrier to resistance, because I do believe it is possible in such a patient to suppress their virus replication indefinitely without concern about resistance, if they take that drug every day as prescribed.

The problem in getting a lot of people to buy into this approach is that, because of coformulation, multiple drug regimens are just as convenient as—or more convenient than—a “simplified” boosted PI regimen. The boosted PI involves at a minimum multiple tablets (in the case of lopinavir/ritonavir) or even multiple prescriptions (in the case of darunavir/ritonavir). So then you have to ask, if a patient is doing well on a coformulated drug like Atripla, where's the simplification? It's not fewer pills. The only real value is that it's fewer pharmacologically active agents and it avoids the potential long-term toxicities of tenofovir, if that's a concern.

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Boosting antiretrovirals without ritonavir

Mascolini: What are the potential advantages of a booster other than ritonavir, and do you see such an agent becoming a clinical reality?

Flexner: The answer to the second question is yes. Gilead is pushing ahead full steam with GS-9350.⁸ They already have it in a trial to boost the integrase inhibitor elvitegravir in combination with tenofovir/emtricitabine⁹ and in another trial comparing it with ritonavir to boost atazanavir.¹⁰ Unless there's some unexpected toxicity with GS-9350, I think there is a high likelihood that it will eventually get approval.

The attraction of a non-ritonavir booster is the possibility of less frequent long-term toxicity, particularly the lipid effects of ritonavir, but also short-term effects: There are some patients who get nausea even with low doses of ritonavir, and there are other rare short-term side effects related to ritonavir. Some people are very supportive of alternatives to ritonavir because they think the pricing might be better. I'm not so sure about that. And there certainly may be advantages with respect to convenience of formulation. For example, the only approved ritonavir formulation (without lopinavir) is the capsule, although it is expected that the tablet will be approved soon. One of the big disadvantages of ritonavir boosting for resource-poor countries is the need to refrigerate the capsule. Presumably that problem will be addressed when the tablet is released.

I already mentioned that a lot of people are excited about moving away from ritonavir because of concerns about long-term toxicity. But there are

so few clinical data on any of the non-ritonavir PK enhancers that I believe there are still many questions about the long-term safety of those drugs. Those questions need to be addressed before we all go rushing off to say that ritonavir is a thing of the past.

Mascolini: Are side effects inescapable when you inhibit a P450 enzyme over a period of years?

Flexner: I don't think that's true. I think the gastrointestinal and lipid side effects from ritonavir are not related to inhibition of cytochrome P450 3A4. There are a number of 3A4 inhibitors on the market, some of them used for chronic diseases, although none of them is nearly as potent as ritonavir. But as far as I can tell, there are no class-specific side effects from inhibiting cytochrome P450 3A4, other than the production of drug interactions.

The evidence I'm aware of suggests that cytochrome P450 3A4 is not responsible for any critical endogenous host-mediated metabolic reactions. In other words it's not responsible for maturing hormones, or for breaking down cytokines, or doing something else to an endogenous host substrate. That suggests to me we can probably inhibit the heck of 3A4 for a long time and not have to worry about what that's doing to the host.

Nanoparticle delivery of antiretrovirals

Mascolini: Is the work on nanoparticle delivery of antiretrovirals far enough along to get a sense of whether it will work?

Flexner: All we can say is that there's one nanoparticle antiretroviral tested in human subjects,

and that's Tibotec's long-acting rilpivirine (Table 5).¹¹ It hasn't gone in to very many human subjects, and Tibotec has had some formulation issues with that product.

I think nanoparticle delivery is a very important concept, particularly as related to the strategy called "test and treat," that is, trying to develop simple ways to go into areas where there is a high incidence of new HIV infections and treating people in high-risk groups to try to block further spread of the virus.¹² I think you're more likely to succeed in doing that if you have very long-acting drugs.

Although this is a very important topic, right now it is strictly a research topic. I don't think we have a product that is anywhere close to a phase 3 study. This is a topic that's going to require a whole lot more activity, and hopefully we'll see something come out of this in the near future.

Prospects for pharmacogenetic-guided therapy

Mascolini: Is pharmacogenetic-guided antiretroviral therapy likely to expand beyond screening for abacavir hypersensitivity?¹³

Flexner: I don't know. I have not seen very many examples of genetic determinants of outcomes for antiretrovirals that are strong enough to suggest to me a high likelihood that it will change the way we prescribe those drugs.

If you want to look at parallels, the closest we have outside the HIV arena for a commonly used drug to treat a chronic condition is the anticoagulant warfarin. And pharmacogenetically guided dosing of warfarin has really not taken off in the clinical practice community for a variety of rea-

sons.¹⁴ I think prescribing physicians need very, very strong evidence about a new diagnostic test, like a genetic polymorphism, before they incorporate it into their practice.

Eradication and its daunting risk/benefit equation

Mascolini: I surveyed 28 clinical investigators for the review article in this issue of RITA! Almost every one of them ranked viral eradication as a top research priority, but almost no one thought eradication would be viable in the next decade. What do you think?

Flexner: Right now it's possible to eradicate HIV from an individual. Unfortunately, I don't think it's possible to do that without a high risk of killing the patient! I believe this is something we're unlikely to see in the next 30 years, except in extraordinary circumstances, for example, people undergoing bone marrow transplantation for non-Hodgkin lymphoma. But I do not believe it's going to be easy to come up with a strategy that will eradicate HIV from an infected individual without enormous potential toxicity and even the risk of fatality.

Given how well tolerated and effective current antiretroviral combinations are, it's going to take some proof to convince patients to go along with this if they think they can take a coformulated drug like Atripla once a day for the rest of their life and have a normal life expectancy. Why on earth would you subject yourself to total lymphoid irradiation and toxic chemotherapy and other things we might have to do, if we can suppress your virus probably indefinitely?

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Mascolini: Relative to HIV vaccine research, how much priority should be given to eradication research?

Flexner: We should keep our eyes open for clever new ideas, and I definitely agree that we should be supporting small studies of clever strategies that have a reasonable likelihood of success. I don't think we should be devoting a

big chunk of our research budgets to the eradication effort, particularly as compared to vaccine research, because I believe an effective HIV vaccine is much more likely to control the epidemic than strategies to eradicate the virus from single individuals who, by the way, might go out and get infected again.

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Table 1. Trials of NRTI-sparing regimens in early therapy: raltegravir/atazanavir

Antiretrovirals (Clinicaltrials.gov identifier)	Sponsor (Sites)	Recruiting?	Trial name and design
Raltegravir + atazanavir ± ritonavir (NCT00874523)	National Centre in HIV Epidemiology and Clinical Research (Australia)	Yes	<p>Raltegravir and Atazanavir Dosing Strategy Study (SPARTA)</p> <p>Arm A: ATV 300 mg + RAL 400 mg twice daily for 4 weeks then ATV 300 mg + RTV 100 mg + RAL 800 mg once daily for 4 weeks</p> <p>Arm B: ATV 300 mg + RTV 100 mg + RAL 800 mg once daily for 4 weeks then ATV 300 mg + RAL 400 mg twice daily for 4 weeks</p>
Raltegravir + atazanavir ± tenofovir + emtricitabine (NCT00931801)	Community Research Initiative of New England (Boston)	Not yet	<p>A Pilot Study of the Novel Antiretroviral Combination of Atazanavir and Raltegravir in HIV-1 Infected Subjects With Virologic Suppression on a Standard Regimen of Boosted Atazanavir, Tenofovir and Emtricitabine (BATAR)</p> <p>Arm 1: ATV/RTV 300/100 mg once daily + RAL 400 mg twice daily</p> <p>Arm 2: ATV 300 mg twice daily + RAL 400 mg twice daily</p> <p>Comparator arm: Continued baseline regimen of ATV/RTV 300/100 mg once daily + TDF/FTC 300/200 mg once daily</p>
Raltegravir + atazanavir (NCT00751153)	Peter J. Ruane (Los Angeles)	Yes	<p>Raltegravir and Atazanavir Replacing Current Suppressive Treatment Because of Side Effects in Current Treatment</p> <p>RAL 400 twice daily + ATV 400 mg daily</p>

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Antiretrovirals (Clinicaltrials.gov identifier)	Sponsor (Sites)	Recruiting?	Trial name and design
Raltegravir + atazanavir ± ritonavir ± tenofovir + emtricitabine (NCT00768989)	Bristol-Myers Squibb, Merck (United States)	No	Phase IIB Pilot of ATV + RAL (SPARTAN) Arm A1: ATV 300 mg twice daily + RAL 400 mg twice daily Arm A2: ATV 300 mg once daily + RTV 100 mg once daily + TDF/FTC 300/200 mg once daily
Raltegravir + atazanavir, other antiretrovirals (NCT00814879)	Yale University, Bristol-Myers Squibb (Connecticut)	Yes	Pilot Study of a Raltegravir Based NRTI-Sparing Regimen Experimental: RAL 400 mg twice daily + ATV 300 mg twice daily Comparator: Standard antiretroviral regimen
For a summary of completed work on nucleoside-sparing first-line or early maintenance regimens, see page 8 of this issue of RITA!			

Table 2. Trials of NRTI-sparing regimens in early therapy: raltegravir/darunavir

Antiretrovirals (Clinicaltrials.gov identifier)	Sponsor (Sites)	Recruiting?	Trial name and design
Raltegravir + darunavir + ritonavir ± tenofovir + emtricitabine (NCT00677300)	Dallas VA Medical Center (Texas)	Yes	Raltegravir And Darunavir Antiretroviral in Antiretroviral-Naive Patients (RADAR) Experimental: RAL 400 mg twice daily + DRV 800 mg once daily + RTV 100 mg once daily Comparator: DRV 800 mg once daily + RTV 100 mg once daily + TDF/FTC 300/200 mg once daily
Raltegravir + darunavir + ritonavir (NCT00830804)	ACTG (United States)	No	Safety and Effectiveness of Raltegravir and Darunavir/Ritonavir in Treatment-Naive HIV-Infected Adults Single arm: RAL 400 mg twice daily + DRV/RTV 800/100 mg once daily

Table 3. Trials of NRTI-sparing regimens in early therapy: raltegravir/lopinavir

Antiretrovirals (Clinicaltrials.gov identifier)	Sponsor (Sites)	Recruiting?	Trial name and design
Raltegravir + lopinavir + ritonavir (NCT00752037)	Saint Michael's Medical Center (New Jersey)	Yes	Safety Study of Lopinavir/Ritonavir With Raltegravir in HIV-Infected Patients Single arm: RAL 400 mg twice daily + LPV/RTV 400/100 mg twice daily
Raltegravir + lopinavir + ritonavir ± tenofovir + emtricitabine (NCT00654147)	University of Miami (Florida)	Yes	Raltegravir + Lopinavir/Ritonavir or Emtricitabine/Tenofovir for HIV Treatment-Naive Subjects Experimental: RAL 400 mg twice daily + LPV/RTV 400mg/100 mg twice daily Comparator: RAL 400 mg twice daily plus TDF/FTC 300/200 mg once daily
Raltegravir + lopinavir + ritonavir; other antiretrovirals (NCT00700115)	Emory University (Georgia)	Yes	Kaletra-Isentress Treatment Evaluation (KITE) Experimental: RAL 400 mg twice daily + LPV/RTV 400/100 mg twice daily Comparator: Continued standard antiretroviral regimen
Raltegravir + lopinavir + ritonavir; efavirenz + tenofovir + emtricitabine (NCT00752856)	California Collaborative Treatment Group (California)	Yes	Raltegravir + Lopinavir/Ritonavir Versus Efavirenz + Tenofovir + Emtricitabine in Treatment-Naive Patients Experimental: RAL 400 mg twice daily + LPV/RTV 400/100 mg twice daily Comparator: EFV + TDF + FTC (as Atripla)
Raltegravir + lopinavir + ritonavir ± tenofovir + emtricitabine	Abbott (United States)	No	Study Comparing Lopinavir/Ritonavir + Emtricitabine/TenofovirDisoproxil Fumarate With a Nucleoside-Sparing Regimen Consisting of Lopinavir/Ritonavir + Raltegravir (PROGRESS) Experimental: RAL 400 mg twice daily + LPV/RTV 400/100 mg twice daily Comparator: LPV/RTV 400/100 mg twice daily + TDF/FTC 300/200 mg once daily

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Table 4. Trials of NRTI-sparing regimens in early therapy: maraviroc/protease inhibitors

Antiretrovirals (Clinicaltrials.gov identifier)	Sponsor (Sites)	Recruiting?	Trial name and design
Maraviroc + darunavir + ritonavir (NCT00993148)	Northwestern University (Chicago)	Not yet	Maraviroc Plus Darunavir/Ritonavir for Treatment-Naive Patients Infected With R5-Tropic HIV-1 (MIDAS) Single arm: MVC 150 mg once daily + DRV/RV 800/100 mg once daily
Maraviroc + darunavir+ ritonavir OR atazanavir OR lopinavir ± tenofovir + emtricitabine (NCT00827112)	Pfizer (United States)	Yes	A Pilot Study Of A Novel Treatment Regimen, Maraviroc + Ritonavir Boosted Atazanavir, In Treatment Naive HIV-Infected Patients Arm A: MVC 150 mg once daily + ATV/RTV (300/100 mg) once daily OR MVC + DRV/RTV 800/100 mg once daily OR MVC + LPV/RTV 400/100 mg twice daily Arm B: TDF/FTC 300/200 once daily + ATV/RTV 300/100 mg once daily OR TDF/ FTC + DRV/RTV 800/100 mg once daily OR TDF/FTC + LPV/RTV 400/100 mg twice daily
Maraviroc + lopinavir + ritonavir (NCT00981318)	Barry M. Rodwick (Florida)	Not yet	Pilot Assessment of Lopinavir/Ritonavir and Maraviroc (PALM) Single arm: MVC 150 mg twice daily + LPV/RTV 400/100 mg twice daily

Table 5. Rilpivirine nanosuspension in 36 HIV-negative volunteers¹¹

- Average rilpivirine nanosuspension particle size 200 nM
- Six panels of 8 healthy adults received 200, 400, or 600 mg of rilpivirine (n = 6) or placebo (n = 2)
- Rilpivirine administered at doses of 200, 400, or 600 mg by intramuscular or subcutaneous injection
- Pharmacokinetic profiles similar after intramuscular and subcutaneous administration
- Intramuscular injection better tolerated
- No serious adverse events or premature discontinuations
- Plasma concentration reached maximum around 3 days
- Plasma concentration fell to 60% of maximum by day 14
- Plasma concentration fell to below 10 ng/mL by 12 to 26 weeks (half-life about 5 weeks)
- Maximum concentration normalized to a 100-mg dose, 20.9 ng/mL
- Area under the curve for week 0 to 12 normalized to a 100-mg dose, 14,500 ng • h/mL
- Pharmacokinetics dose-proportional
- Intersubject variability low
- **Once monthly 600 mg of rilpivirine nanosuspension predicted to achieve troughs similar to 25 mg of oral rilpivirine once daily**



One HIV Clinician's Toughest Challenges

An interview with **Steven G. Deeks, MD**

*Professor of Medicine in Residence
University of California, San Francisco
San Francisco, California*

Getting HIV-infected people into care

Mascolini: How hard is it to get people with HIV tested and into care?

Deeks: From my perspective with patients in San Francisco, where the epidemic is still largely driven by men who have sex with men, everyone is aware of their potential HIV risk, everyone has access to testing, and nearly everyone has easy access to treatment. Yet there still is a large, poorly defined proportion of people in San Francisco who, despite being at risk, choose not to get tested.

There's also a large proportion of people who are infected and have access to therapy but don't show up at the clinic until their CD4 count is quite low. These are profound barriers to care, and I'm not entirely sure how we're going to address them from a systems perspective because they're really behavioral issues.

Mascolini: Do people make an active choice not to get tested, or do they just let things slide too long?

Deeks: My personal feeling is there's probably a little bit of both. There's certainly a fair amount of denial: some people would rather just not deal with it. To some degree, that's human nature. There are probably also people who are actively opposed to starting therapy because it's perceived to be toxic and inconsistent with their approach to life.

Mascolini: What do you think about the CDC recommendation that everyone between 13 and 64 years old be offered HIV testing when they seek medical care (Table 1)?¹

Deeks: It makes great sense because probably the best way to slow down the spread of the epidemic is for more people to know their status, which is particularly true with lower-risk populations.

But universal testing is problematic. Some of the most heart-wrenching experiences I've had as an HIV clinician involve people who've undergone testing despite being at low risk and had quirky, difficult-to-interpret test results. This results in a tremendous amount of stress. I've even known a few cases of people who ended up on therapy even though they turned out to be HIV-negative.

Table 1. CDC recommendations on HIV screening in adolescents and adults¹

<ul style="list-style-type: none"> In all health-care settings, screening for HIV infection should be performed routinely for all patients aged 13-64 years. Health-care providers should initiate screening unless prevalence of undiagnosed HIV infection in their patients has been documented to be less than 0.1%. In the absence of existing data for HIV prevalence, health-care providers should initiate voluntary HIV screening until they establish that the diagnostic yield is less than 1 per 1000 patients screened, at which point such screening is no longer warranted.
<ul style="list-style-type: none"> All patients initiating treatment for tuberculosis should be screened routinely for HIV infection.
<ul style="list-style-type: none"> All patients seeking treatment for sexually transmitted diseases (STDs), including all patients attending STD clinics, should be screened routinely for HIV during each visit for a new complaint, regardless of whether the patient is known or suspected to have specific behavior risks for HIV infection.

When you test everybody, including those with basically no risk, the proportion of people who are false-positive goes way up. And a false-positive HIV test has harm—psychological harm and (rarely) medical harm. It doesn't mean we shouldn't be doing it, but it is a concern.

Solving HIV/HCV coinfection conundrums

Mascolini: Why is caring for HCV-coinfected people such a challenge?^{2,3}

Deeks: For two reasons: First, coinfecting people often get infected with both viruses because of injection drug use, and that complicates everything. In this way, the coinfecting population differs from people infected only with HIV. But the major issue is HCV therapy (Table 2). The drugs we have now to treat HCV are quite toxic, and they're often not that effective, at least for the

types of HCV viruses we see most often. So we've had very limited success in getting people in our clinic onto HCV therapy and cured or even improved as a consequence of treatment.

Mascolini: You mean the HCV genotype you see most is the one that doesn't respond well to interferon/ribavirin, HCV 1?⁴

Deeks: Right. Our patients often don't have treatment-susceptible genotypes (types 2 and 3), and, even if they do, the toxicity of the drugs prevents people from being maintained on these drugs for a sufficient period of time. Ultimately, when there are better-tolerated and more effective drugs, it's my sense that the treatment of HCV will be very different from the treatment of HIV because HCV will be effectively cured with short-term regimens. So this obsession with drugs that are once-a-day drugs or with drugs that

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Table 2. US guidelines for treating HCV infection in patients with HIV*

In the absence of contraindications to pegylated interferon or ribavirin, treatment for HCV infection should be offered routinely to persons in whom the potential benefits of therapy are judged to outweigh the potential risks, including (but not limited to) persons with the following conditions:

- HCV genotype 2 or 3 infection
- HCV genotype 1 infection with a low HCV RNA level (<800,000 IU/mL) (although certain specialists might not recommend treatment of patients with HCV genotype 1 infection and low or intermittently undetectable HCV RNA, response to pegylated interferon plus ribavirin is improved in those with HCV RNA levels <800,000 IU/mL compared with those with levels above this threshold, which might favor treatment in this group)
- Significant hepatic fibrosis (bridging fibrosis or cirrhosis)
- Stable HIV infection not requiring antiretroviral therapy
- Acute HCV infection (<6 months' duration)
- Cryoglobulinemic vasculitis
- Cryoglobulinemic membranoproliferative glomerulonephritis
- Strong motivation to treat their HCV infection

*From Kaplan JE, Benson C, Holmes KK, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. *MMWR Morb Mortal Wkly Rep.* 2009;58(RR04):1-198. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5804a1.htm>.

have zero side effects in the HIV world probably will not apply to the HCV world because those drugs have to be taken only for a limited period of time.

Controlling MDR virus when new drugs fall short

Mascolini: With several new antiretrovirals active against multidrug-resistant (MDR) virus (darunavir, etravirine, raltegravir, maraviroc, en-

fuvirtide), is managing people with MDR virus still a big challenge?

Deeks: Yes. Clearly the MDR deep-salvage situation has improved dramatically in the past few years. There's probably been a 10-fold reduction in the number of people in San Francisco who have highly resistant HIV and essentially no viable options for complete viral suppression. These individuals are out of options because they got to these new drugs too late and/or because they simply can't adhere to the drugs.

Depending on how you define it, in our cohort we have anywhere from 30 to 50 people who no longer have any options for complete viral suppression. This is a low number compared to 3 years ago. Of course these individuals take up a disproportionate amount of the time we spend in clinic because they have such a complicated set of issues. So from my perspectives MDR virus is still one of the bigger problems in the clinic.

Mascolini: What proportion of your clinic population do those 30 to 50 people represent?

Deeks: I should be careful to distinguish between our cohort study, which has sought to enroll patients with multidrug-resistant HIV, and our clinic, which is more representative. I suspect that the prevalence of multidrug-resistant HIV in our clinic is less than 5%.

Mascolini: So what do you do with those people?

Deeks: We often do what we did in the past, which is to maintain them on their nucleoside analogs because of their partial antiviral activity. We maintain them on protease inhibitors because of some possible CD4 benefit, and we consider maintaining them on an integrase inhibitor or enfuvirtide or maraviroc for some immunologic benefit. Essentially, we try to tailor their regimen to slow down disease progression while waiting for more treatment options.

Deciding on tenofovir vs abacavir vs no NRTIs

Mascolini: At the other end of the treatment spectrum, for people with little or no treatment experience, what's your thinking on using abacavir versus tenofovir versus NRTI-sparing regimens?

Deeks: I think ultimately we need viable nucleoside analog-free regimens. This is one of the great unmet needs of HIV medicine.

Right now, for a person starting therapy I would generally prefer tenofovir over abacavir, because of both perceived safety^{5,6} and virologic efficacy⁷ issues with abacavir versus tenofovir. Certainly if I'm using efavirenz I will use tenofovir (with emtricitabine) in a fixed-dose combination regimen. But in a person who has certain comorbid conditions, especially those involving kidney function, I'm often torn. In that situation I still use a fair amount of abacavir.

Understanding inflammation, CNS disease, and non-AIDS diagnoses

Mascolini: Do you try to construct regimens that presumably penetrate the central nervous system (CNS) well?

Deeks: In the past I've been under the impression—based on some local expertise—that we should ignore concerns about CNS penetration and get the plasma viral load undetectable, because essentially every time the viral load is undetectable in plasma, it's undetectable in cerebrospinal fluid. And that approach has clearly done well: people don't get dementia and other CNS complications, as they did in the past.

But now that my goals of therapy are no longer just to prevent AIDS but truly to restore health, prolong life, and allow my patients the same kind of long-term outcome that an HIV-negative person has, then, yes, some of the more subtle things become more of a concern in planning antiretroviral therapy. Subtle effects on kidney function, liver function, heart function, inflammation—

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these things do affect the way I think about these drugs.⁸⁻¹⁰

I now believe one of the major factors in HIV care may be this issue of accelerated changes in mental status that are not simply explained by a patient's pre-HAART condition, but by some ongoing injury during therapy. I'm not absolutely convinced this ongoing injury is happening. But if it is occurring, I'm certainly willing to consider that it is due to persistent viral replication in the CNS and hence amenable to drugs with greater CNS penetration.¹¹ But this has not yet affected the way I prescribe drugs.

Mascolini: How concerned are you about ongoing inflammation and non-AIDS diseases in people on antiretroviral therapy, and how should

HIV clinicians factor these issues into their treatment plans?

Deeks: I think the facts are pretty straightforward: HIV-infected people on therapy have a higher risk for these non-AIDS conditions than people who are HIV-negative.¹²⁻¹⁶ That's a fact. In addition, HIV-associated inflammation is dramatically reduced but often not normalized by antiretroviral therapy.¹⁷ This is also a fact. Finally, I think it is likely that this inflammation during therapy is contributing to these non-AIDS events in our HIV-infected patients, just as persistent inflammation is harmful in uninfected persons.¹⁷⁻²⁰ So essentially there is a problem, and it's probably related to inflammation. How big the problem is and what to do about it are not yet clear.

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