Don’t Ditch the Gym After 60 (or 80)

The Invisible Effects of Your Workout Are Even More Important As We Age

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TL;DR: Aging and ARVs (especially integrase inhibitors and tenofovir) both erode insulin sensitivity, bone density, and cardiovascular health. But 20-30 minutes of resistance training three times a week does something many don’t realize: it directly activates vitamin D receptors in muscle and bone, keeps glucose transporters working for hours afterward, stimulates a bone hormone (osteocalcin) that supports insulin sensitivity and cognition, and upregulates your body’s antioxidant defenses. Yoga adds cortisol reduction (i.e., help for your bone, sleep & hormones) and autonomic rebalancing. Walking supports blood vessel function and brain health. Twice-daily meditation is nothing short of miraculous. Common genetic variants (testable for as little as $200) can reveal whether your vitamin D pathway or nitric oxide system is running at reduced capacity, information that sharpens which interventions matter most for your specific genetic blueprint. Links: IG, DFH, MBL, SP, XY, FS.

Most people have heard the basics: exercise is good, vitamin D matters, bone density a concern. But very few know *why* these things are connected at the molecular level, or how the specific medications keeping them alive may be quietly reshaping their metabolic landscape in ways that standard lab work doesn’t capture.

This post is about what’s happening beneath the surface, and what can be done about it with lifestyle alone. (A future post will cover food and supplement strategies.)

The Midlife Metabolic Shift Nobody Ever Tells You About

As we age, insulin sensitivity declines-- for EVERYONE. Muscle cells become less responsive to insulin’s signal to absorb glucose from the bloodstream. The result: higher circulating blood sugar, more insulin required to do the same job, and eventually a metabolic environment that accelerates aging across every organ system, from brain to bone to cardiovascular.

For HIV-positive folks on antiretroviral therapy, this process can be sort of turbo charged. Integrase inhibitors (bictegravir, dolutegravir), now lamentably the star players of most regimens, bring with them weight gain, insulin resistance, and dyslipidemia. Tenofovir alafenamide (TAF), which has largely replaced the older tenofovir disoproxil fumarate (TDF) due to its disingenuous and shamelessly promoted “superior safety” profile, is itself independently associated with weight gain

and lipid changes. So the very medications “sustaining life” are at the same time fast-tracking metabolic aging. But it’s not all bad news: just as for our HIV-, non-chronically medicated brethren, there are harm reduction measures one can take.

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Vitamin D: More Complicated Than “Take a Supplement”

Vitamin D, of course, is not actually a vitamin; it’s a hormone. But then you already knew that, smarty pants. Its receptor (VDR) is expressed in virtually every tissue: bone, brain, muscle, gut, immune cells, endothelium, kidney. When vitamin D binds VDR, it activates the transcription of over 1,000 genes . Calcium metabolism, yes, but also immune regulation, cell differentiation, neuroprotection (geek out here). (Vit-D downregulates Th1 and Th17 adaptive immunity, so if you notice a herpes (or other viral infection) outbreak when you take more than a little vitamin D as supplement, that’s likely why; geek out here.)

For folks on tenofovir (whether TDF or TAF), vitamin D status deserves closer attention than it typically gets. TDF in particular has been associated with impaired renal activation of vitamin D (the kidney converts the storage form, 25-OH, into the active hormonal form, 1,25-dihydroxy). Even TAF, though said to be gentler on the kidneys overall, operates in an immunological and metabolic context that can also affect vitamin D utilization.

HIV infection itself adds another layer. Multiple studies have shown that HIV can “epigenetically silence” the VDR gene in T cells through promoter methylation, meaning the receptor protein is produced in reduced quantities even when circulating vitamin D levels are adequate. The result: vitamin D is in the bloodstream, but the cellular machinery to use it is operating at reduced capacity.

HIV infection “epigenetically silences” the vitamin D receptor (VDR) gene. You may have plenty of D in your bloodstream, but the cellular machinery to use it ... is in sleep mode.

Two common gene variants directly affect how well an individual produces and responds to vitamin D:

CYP2R1 is the liver enzyme responsible for the first activation step of vitamin D (converting it from cholecalciferol to the 25-OH storage form measured on standard blood tests). A common variant reduces this enzyme's efficiency. People carrying it need more vitamin D input (fatty fish, maitake mushrooms, egg yolks are top sources) to achieve the same serum level. For someone already on medications that accelerate vitamin D catabolism, this genetic handicap narrows the margin further.

VDR FokI is a variant in the vitamin D receptor itself. The T allele produces a longer, less transcriptionally active receptor protein. A man who carries one or two copies of the T allele (roughly 40-50% of people of European-ancestry carry at least one) has intermediate or reduced VDR signaling, meaning that even adequate serum vitamin D may not translate into full downstream biological effect in bone, brain, or immune cells.

Neither of these variants is rare. Neither is tested on standard blood work. Both are available through direct-to-consumer genetic panels, including the glossy 3x4 Genetics Blueprint, although only the tests using Opus 23 or similar software also analyze interactions among different SNPs. For that reason, I kind of prefer the Spotlight™ kits (although 3x4's glossy, color "Genetic Blueprint" reports are lovely). Knowing whether these variants or others are present can fundamentally change how a person approaches his or her health-- or life, for that matter.

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The Third Variant: Your Blood Vessels

There is a third genetic variant worth knowing about, and it affects something even more fundamental than vitamin D: nitric oxide (NO).

NO is the primary signaling molecule of the endothelium, the tissue lining every blood vessel in the body. It regulates vasodilation (blood flow), blood pressure, platelet aggregation, and vascular inflammation. It also operates in the brain (regulating cerebral blood flow and neurotransmission), the gut (regulating motility and mucosal barrier integrity), the kidneys (regulating filtration and blood flow), and bone (regulating osteoblast activity).

The enzyme that produces NO in blood vessels is endothelial nitric oxide synthase (eNOS), encoded by the NOS3 gene. A common promoter variant, NOS3 -786 T>C, reduces the amount of eNOS enzyme produced. People who carry two copies of the reduced-expression allele (an estimated 35-50% of folks of European-ancestry) may have roughly 40-50% less eNOS output than those with the standard genotype. Their blood vessels still work, but the signaling molecule that keeps them open, flexible, and anti-inflammatory is running at reduced capacity.

People who carry two copies of the relatively common NOS3 -786 T>C have 40-50% less eNOS output than those with the standard genotype.

For an HIV-positive person on ARVs, with HIV-associated chronic inflammation, possible metabolic syndrome from integrase inhibitors, and decades of immune activation, a genetically undertoned NO pathway is not just a SNP that precision medicine aficionados like me geek out on. It's a systemic vulnerability affecting every organ that depends on blood flow; in other words, every organ.

There are actually NO saliva test strips these days. Imagine they are on the Bezos behemoth. You can also snag them here. Use code FIRST25 to get them for even less.

What Exercise Actually Does: "Burning Calories" Is the Least of It

Here is what most folks, including many clinicians, don't know: exercise doesn't just burn glucose and build muscle. Itactivates hormone receptors, antioxidant defense systems, and signaling pathways at the molecular level. But the magnitude of effects depends on what kind of exercise is performed.

Resistance training (weight machines, free weights, bodyweight exercises targeting large muscle groups) is the most potent stimulus for several pathways simultaneously. It upregulates VDR expression in skeletal muscle, meaning the muscle produces more vitamin D receptor protein, increasing the tissue's responsiveness to whatever vitamin D is circulating. It upregulates androgen receptors in the loaded muscles. It activates the IGF-1/Akt pathway, which keeps glucose transporters (GLUT4) at the muscle cell surface for hours after the session, pulling glucose out of the bloodstream. It stimulates osteoblasts to release osteocalcin, a bone-derived hormone now recognized to improve insulin sensitivity, support testosterone production, and cross the blood-brain barrier to support memory and cognition. And it activates Nrf2, the master switch for the body's antioxidant defense system.

A 20-30 minute session, three times per week, targeting large muscle groups (leg press, chest press, lat pulldown, seated row) at moderate load (12-15 repetitions with good form, not chasing failure) is sufficient to activate these pathways. For people over 60, especially those with connective tissue considerations (there are key SNPs to know too to inform you about your individual risk for such injuries!), moderate weight and controlled tempo are safer and nearly as effective as heavier loads.

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activates VDR in muscle and bone, keeps glucose transporters working, boosts insulin sensitivity, and upregulates the body’s antioxidant defenses.

In one cool study, the key glucose transporter GLUT4 remained elevated at the muscle cell surface for over 3 hours after resistance exercise-- but returned to baseline much sooner after aerobic exercise. The mechanism was a pathway (IGF-1/Akt/AS160) that only resistance exercise activated. For aging men concerned about insulin sensitivity, this is a meaningful distinction.

Yoga (particularly styles emphasizing sustained holds, such as Iyengar or Hatha) contributes something resistance training cannot: direct upregulation of brain GABA levels (the primary inhibitory neurotransmitter), measurable cortisol reduction, and autonomic nervous system training. For men whose stress response is running hot, whether from decades of living with HIV, the psychological weight of chronic illness, toxic politics, money worries, care-giving responsibilities, or the ambient stress of contemporary life, yoga addresses the neuroendocrine axis that resistance training does not. Sustained standing poses also provide weight-bearing stimulus for bone, though at lower force levels than gym-based resistance work.

Walking (2 miles, roughly 40 minutes at moderate pace) contributes steady-state eNOS upregulation in blood vessels (relevant for men with reduced NOS3 function), sustained BDNF elevation for brain health, lymphatic circulation for immune surveillance, and fat oxidation. It is the gentlest daily maintenance for the cardiovascular and cerebrovascular systems, with essentially no injury risk and no cortisol cost.

These three modalities are complementary, not interchangeable. Each activates different molecular pathways. A practical weekly schedule might include three gym sessions (20-30 minutes each), two 60-90 minute yoga classes, and daily walking. The combination covers VDR upregulation, glucose disposal, bone formation, NO support, cortisol management, autonomic balance, and brain-derived neurotrophic factor.

Meditation... Truly Turns Back Time (cue the Pop Goddess)

Twice-daily meditation (even 10-15 minutes per session) has been shown in multiple randomized controlled trials to reduce cortisol, the stress hormone that, when chronically elevated, suppresses immune surveillance, impairs bone formation, disrupts sleep architecture, and may increase hepatic production of sex hormone-binding globulin (SHBG), the protein that binds testosterone and reduces its bioavailability.

For people who carry a higher burden of chronic immune activation and psychosocial stress than the general population, cortisol management is a physiological intervention with measurable downstream effects on the very systems (immune, skeletal, metabolic, cardiovascular) that HIV

medicines put at risk.

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The Takeaway

The most highly prescribed medications for HIV are are also metabolically active in ways that compound the normal effects of aging on insulin sensitivity, bone density, vitamin D metabolism, and cardiovascular health. Lifestyle interventions, specifically resistance training, yoga, walking, and meditation, activate molecular pathways (VDR, GLUT4, androgen receptors, eNOS, Nrf2, osteocalcin, GABA, BDNF) that directly counteract these effects. Rather than optional "wellness" add-ons, I would argue that they are "must-do," enlightened self-care physiological countermeasures.

Genetic testing can identify whether specific variants (CYP2R1, VDR FokI, NOS3, and those tendon/collagen SNPs I alluded to, among others) are amplifying an individual's vulnerability. This information doesn't change the lifestyle recommendations, but it sharpens them: a man who knows his VDR is genetically less responsive, or his NO pathway is genetically undertoned, can prioritize the specific interventions that address his specific bottlenecks.

None of this requires a gym membership that costs more than the medications (although I'm kind of loving TMPL and Gold's dtLA, now EoS). It requires understanding what's happening at the cellular level, and acting on it.

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