PIPELINE REPORT 2012

HIV
HCV
TB

Drugs, Diagnostics, Vaccines, & Preventive Technologies in Development

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ABOUT HIV i-BASE

HIV i-Base is a London-based HIV treatment activist organization. HIV i-Base works in the United Kingdom and internationally to ensure that people living with HIV are actively engaged in their own treatment and medical care and are included in policy discussions about HIV treatment recommendations and access.

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ABOUT TAG

The Treatment Action Group (TAG) is an independent AIDS research and policy think tank fighting for better treatment, a vaccine, and a cure for AIDS. TAG works to ensure that all people with HIV receive lifesaving treatment, care, and information.

www.treatmentactiongroup.org

2012 PIPELINE REPORT

HIV, HEPATITIS C VIRUS (HCV), AND TUBERCULOSIS (TB)
DRUGS, DIAGNOSTICS, VACCINES, AND PREVENTIVE TECHNOLOGIES
IN DEVELOPMENT

By Polly Clayden, Simon Collins, Colleen Daniels, Nathan Geffen, Mark Harrington, Richard Jefferys, Coco Jervis, Karyn Kaplan, Erica Lessem, and Tracy Swan

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By Polly Clayden and Mark Harrington

> In nine countries, we enrolled 1763 couples in which one partner was HIV-1–positive and the other was HIV-1–negative; 54% of the subjects were from Africa, and 50% of infected partners were men. HIV-1–infected subjects with CD4 counts between 350 and 550 cells per cubic millimeter were randomly assigned in a 1:1 ratio to receive antiretroviral therapy either immediately (early therapy) or after a decline in the CD4 count or the onset of HIV-1–related symptoms (delayed therapy). The primary prevention end point was linked HIV-1 transmission in HIV-1–negative partners. The primary clinical end point was the earliest occurrence of pulmonary tuberculosis, severe bacterial infection, a World Health Organization stage 4 event, or death….As of February 21, 2011, a total of 39 HIV-1 transmissions were observed (incidence rate, 1.2 per 100 person-years; 95% confidence interval [CI], 0.9 to 1.7); of these, 28 were virologically linked to the infected partner (incidence rate, 0.9 per 100 person-years, 95% CI, 0.6 to 1.3). Of the 28 linked transmissions, only 1 occurred in the early-therapy group (hazard ratio, 0.04; 95% CI, 0.01 to 0.27; $P<0.001$). Subjects receiving early therapy had fewer treatment end points (hazard ratio, 0.59; 95% CI, 0.40 to 0.88; $P=0.01$). The early initiation of antiretroviral therapy reduced rates of sexual transmission of HIV-1 and clinical events, indicating both personal and public health benefits from such therapy.
>
> —MS Cohen et al.[1]

> The fact that treatment of HIV-infected adults is also prevention gives us the wherewithal, even in the absence of an effective vaccine, to begin to control and ultimately end the AIDS pandemic....For the first time in the history of HIV/AIDS, controlling and ending the pandemic are feasible; however, a truly global commitment...is essential. Major investments in implementation now will save even greater expenditures in the future; and in the meantime, countless lives can be saved.
>
> —AS Fauci[2]

> The yearly cost of achievement of universal access to HIV prevention, treatment, care, and support by 2015 is estimated at no less than US$22 billion. Implementation of the new investment framework would avert 12.2 million new HIV infections and 7.4 million deaths from AIDS between 2011 and 2020 compared with continuation of present approaches, and result in 29.4 million life-years gained. The framework is cost effective at $1060 per life-year gained, and the additional investment proposed would be largely offset from savings in treatment costs alone.
>
> —B Schwartländer et al.[3]

Introduction

Three papers published in the past year[4,5,6] provide the scientific, public health, and policy framework for accelerating the response to the HIV pandemic such that within a few years the spread of HIV can be reversed, saving millions of lives and billions of dollars, using existing antiretroviral therapy (ART) introduced earlier and more broadly around the world. The only thing holding us back is the lack of economic and political leadership at the highest levels.

Juxtaposed against a background of economic distress and political paralysis in the world's rich countries not seen since the early 1930s, the abundance of promising advances documented in this year's i-Base/TAG *2012 Pipeline Report* may seen unattainably out of reach to many of the millions of people who need them most. It will be the task of the activists, implementers, policy makers, and scientists attending this year's International AIDS Conference in Washington, D.C., to work together to turn the tide so that everyone who needs high-quality treatment and prevention interventions for the global HIV, hepatitis C virus (HCV), and tuberculosis (TB) pandemics receives them.

Since the results of HPTN 052 were released last year,[7] HIV prevention and treatment research have moved ever forward; the interventions that have saved over 7 million people's lives since the advent of highly active antiretroviral therapy (HAART) in 1996 are also proving to be remarkably powerful as HIV prevention measures. The HPTN 052 study set a very high bar for performance, as the measured 96% reduction in HIV transmission was built upon a high-quality clinical trial design and implementation, good prevention practice in both arms, and evidently very high adherence rates.

Although with less dramatic effect than HPTN 052, results of CAPRISA 004[8] (which used tenofovir as a topical vaginal microbicide, like some other preexposure prophylaxis [PrEP] studies such as iPrEx[9] which were released in the past two years, show that antiretrovirals can also offer protection when used by an HIV-negative partner, although the optimal use of these interventions is as yet uncertain. Table 1 shows the hierarchy of effect from clinical trial evidence using antiretrovirals for preventing sexual HIV transmission. But with all these studies, it is clear that adherence is required for treatment-as-prevention to work. Similarly, early studies in the HAART era showed that over 90% adherence was required for durable virological suppression among those taking treatment as treatment.

TABLE 1. Clinical Trial Evidence Using Antiretrovirals for Preventing HIV Infection

Study	Effect Size % (CI)
Treatment for prevention (HPTN 052)	96% (73–99)
PrEP for serodiscordant couples (Partners PrEP)	73% (49–85)
PrEP for heterosexuals (Botswana TDF 2)	63% (21–48)
PrEP for men who have sex with men (iPrEx)	44% (15–63)
Microbicide (CAPRISA 044 tenofovir gel)	39% (6–60)

Source: Abdool Karim SS. CAPRISA 004 two years on: ten key lessons and their implications. Keynote address presented at: 2012 International Microbicides Conference; 2012 April 15; Sydney, Australia. Available from: http://www.microbicides2012.org/images/pdfs/m2012%20-%20abdool%20karim%20-%20caprisa%20004%20lessons.pdf. (Accessed 2012 July 3)

The potential contribution of these new discoveries to reduce the spread of HIV is directly threatened by today's interlinked political and economic crises. Although a few administrative areas, such as the Canadian province of British Columbia and the city of San Francisco, California, have begun to provide universal offers of HIV treatment to all those referred to care, no country has yet started to fully implement these new interventions. The U.S. federal HIV treatment guidelines panel updated its recommendations in spring 2012 to recommend the universal offer of antiretroviral therapy (ART) to those with CD4 counts over 500 cells/mm^3,[10] but it is too soon to assess whether this change is affecting practice in the United States. The panel's recommendation is based on disease stage, and its statement of the primary (therapeutic) and secondary (preventive) benefits of ART, and the evidence base for this recommendation is worth reading in full:

> The primary goal of antiretroviral therapy (ART) is to reduce HIV-associated morbidity and mortality. This goal is best accomplished by using effective ART to maximally inhibit HIV replication, as defined by achieving and maintaining plasma HIV RNA (viral load) below levels detectable by commercially available assays. Durable viral suppression improves immune function and quality of life, lowers the risk of both AIDS-defining and non-AIDS-defining complications, and prolongs life. Based on emerging evidence, additional benefits of ART include a reduction in HIV-associated inflammation and possibly its associated complications.
>
> The results of a randomized controlled trial and several observational cohort studies demonstrated that ART can reduce transmission of HIV. Therefore, a secondary goal of ART is to reduce an HIV-infected individual's risk of transmitting the virus to others.

Although the Panel concurs that this public health benefit of ART is significant, Panel recommendations on when to initiate ART are based primarily on the benefit of treatment to the HIV-infected individual.

The strength of Panel recommendations depends on disease stage. Randomized controlled trials provide definitive evidence supporting the benefit of ART in patients with CD4 counts <350 cells/mm^3. Results from multiple observational cohort studies demonstrate benefits of ART in reducing AIDS- and non-AIDS-associated morbidity and mortality in patients with CD4 counts ranging from 350 to 500 cells/mm^3. The Panel therefore recommends ART for patients with CD4 counts =500 cells/mm^3 (AI for CD4 count <350 cells/mm^3 and AII for CD4 count 350 to 500 cells/mm^3).

The recommendation to initiate therapy at CD4 count >500 cells/mm^3 (BIII) is based on growing awareness that untreated HIV infection or uncontrolled viremia may be associated with development of many non-AIDS-defining diseases, including cardiovascular disease (CVD), kidney disease, liver disease, neurologic complications, and malignancy; availability of ART regimens that are more effective, more convenient, and better tolerated than earlier ART combinations no longer widely used; and evidence from one observational cohort study that showed survival benefit in patients who started ART when their CD4 counts were >500 cells/mm^3.

Tempering the enthusiasm to treat all patients regardless of CD4 count is the absence of randomized data that definitively demonstrate a clear benefit of ART in patients with CD4 count >500 cells/mm^3 and mixed results on the benefits of early ART from observational cohort studies. In addition, potential risks of short- or long-term drug-related complications and nonadherence to long-term therapy in asymptomatic patients may offset possible benefits of earlier initiation of therapy. When resources are not available to initiate ART in all patients, treatment should be prioritized for patients with the lowest CD4 counts and those with the following clinical conditions: pregnancy, history of an AIDS-defining illness, HIV-associated nephropathy (HIVAN), or HIV/hepatitis B virus (HBV) coinfection.[11]

In any case, with over two thousand Americans in nine states currently on AIDS Drug Assistance Program (ADAP) waiting lists,[12] the availability of HIV treatment *as treatment* for all HIV-positive residents of the United States is far from universal. It is unlikely that the preventive benefits of HIV treatment can be fully obtained until HIV treatment *as treatment* is available for everyone.

Last month's unexpected U.S. Supreme Court decision to uphold the Affordable Care Act (ACA) provides a strong foundation for expanding HIV—as well as HCV—treatment, care, and prevention through the expansion of health coverage through both private insurance and public-sector Medicaid expansion. Over the next year, activists, policy makers, and researchers must build the foundation for the ACA and its accompanying health care expansion to underwrite the provision of universal voluntary treatment on demand for all people in the United States living with HIV and/or HCV infection.

Globally, the situation is grimmer. The past year saw the cancellation of the 11th round of funding by the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), the forced resignation of its highly respected executive director, pioneering AIDS researcher and activist Dr. Michel Kazatchine, his replacement by an unemployed Colombian banker named Gabriel Jaramillo, and the subsequent firing of many of the Global Fund's staff. It's not clear who has pulling the strings in this badly conducted Global Fund restructuring, but it is clear that the result has been a significant retardation of its programming. In the meantime, President Obama's 2013 budget proposes to cut $550 million from the President's Emergency Plan for AIDS Relief (PEPFAR), with a potentially dire impact on millions of people who are benefiting from PEPFAR programs.

We have been documenting President Obama's disappointing record on AIDS since 2009.[13,14] More recently, his administration's lack of support for PEPFAR[15] threatens to undermine its impending legislative reauthorization, due in 2013.

Support for global HIV and tuberculosis (TB) programs from European countries such as France, Ireland, the Netherlands, and the United Kingdom, which have been significant donors to global health over the past decade, have been undermined during the past four years of economic turbulence. Meanwhile, the European Union (EU) superpower Germany, which has been a global-health deadbeat over the past decade, is now turning the screws on its own EU Mediterranean members, with predictably grim results for health: last year saw the first recrudescence of malaria in Greece since the disease was eliminated in 1974;[16] while in Athens, the cancellation of needle-exchange programs resulted in a whopping 1,250% increase in new HIV infections in the first ten months of 2011 compared with the previous year.[17] (Astonishingly, late last year President Obama signed a reinstatement of the U.S. federal ban on needle-exchange funding as part of the 2011 budget deal with Congress.[18]) Seemingly everywhere in the so-called developed world, governments calculate politically and impose relentless economic austerity on their populations, regardless of the cost to health or lives. The consequences for their own citizens and for those who live in less developed nations will be high.

In some developing countries, however, domestic political will has coalesced around moving in a more positive and life-saving direction. After a titanic struggle going back to 1998, the Republic of South Africa initiated public-sector ART in 2003. More recently, following the departure of President Thabo Mbeki, whose regime and its institutionalized denial that HIV causes AIDS has been estimated to have led to at least 330,000 preventable deaths,[19] the current health minister, Dr. Aaron Motsoaledi, is administering an unprecedented rollout of HIV and TB testing and treatment with the goal of halving new HIV infections, achieving 80% HIV treatment coverage, and halving new TB infections and deaths by the year 2015.[20]

South Africa now has more people on HIV treatment than the United States has people living with HIV, and has the biggest ART program in the world. The country has made significant strides in reducing drug prices, decentralizing HIV care and treatment, and switching first-line therapy from stavudine; however, much more progress remains to be made in order to completely eliminate mother-to-child HIV transmission, treat pediatric HIV, and increase retention in care.[21] Moreover, the South African government is now paying for most of its HIV treatment program with domestic funds, replacing much of the scale-up support provided by PEPFAR and the Global Fund. However, this is unusual in most African countries or for that matter most developing ones.

All is not wine and roses in South Africa, however, as Nathan Geffen's commentary (below at page 17) indicates, its National Strategic Plan has inspiring and aspirational goals, particularly compared with the Obama administration's anemic National HIV/AIDS Strategy for the United States' objectives to:

- lower new HIV infections by 25%;
- reduce HIV incidence by 30%;
- increase Americans' knowledge of their own serostatus from 79% to 90%;
- increase the proportion of newly diagnosed patients linked to clinical care within three months of their HIV diagnosis from 65% to 85%;
- increase the proportion of Ryan White HIV/AIDS program clients who are in continuous care (at least two visits for routine HIV medical care in 12 months at least 3 months apart) from 73% to 80%;
- increase the percentage of Ryan White HIV/AIDS program clients with permanent housing from 82% to 86%; and
- increase the proportion of HIV-diagnosed gay and bisexual men, Blacks, and Latinos/Latinas with undetectable viral load by 20% each,

all by the end of 2015.[22]

The U.S. Centers for Disease Control and Prevention (CDC) estimates that between 48,000 and 56,000 Americans become infected with HIV each year.[23] Reducing this by the target of 25–30% would reduce new infections by 14,000–18,400 by the end of 2015, leaving 37,600–42,000 new infections each year by 2015.

The CDC estimates that only 28% of all Americans with HIV have an undetectable viral load.[24] Thus, increasing this by 20% in absolute terms would mean that 48% of HIV-positive Americans had an undetectable viral load by the end of 2015, leaving 52% of them with detectable HIV, and the risk of progression and onward transmission. (Another report suggests that just 19% of Americans with HIV have an undetectable viral load, which would result in coverage by 2015 being even lower.[25])

Even assuming the CDC's estimate that 28% of HIV-positive Americans have an undetectable viral load, the status quo is unacceptable, and the full achievement of the National AIDS Strategy's uninspiring goals will leave a huge cost to future generations in dollars, health, and lives.

> Only an estimated 28% of all HIV-infected persons in the United States are virally suppressed, largely because even among those with diagnosed infection, only 51% are receiving regular HIV care. Without substantial improvement in these percentages, 1.2 million new HIV infections would be expected to occur in the United States over the next 20 years.[26] Based on estimated lifetime HIV treatment costs of $367,000 per person (2009 dollars)[27] caring for persons who become infected could cost as much as $450 billion in health-care expenditures.[28,29]

One reason for the failure of the U.S. National AIDS Strategy to focus on more ambitious goals is the administration's preemptive requirement that few to no additional resources be expended in the domestic fight against HIV. A recent publication indicates that without significant and immediate scale-up of HIV prevention, testing, and treatment, "key goals of the NHAS will soon be epidemiologically out of reach."[30]

As noted above, however, the recent decision upholding the constitutionality of the ACA provides a framework for achieving universal voluntary treatment on demand in the United States for those with either or both HIV and HCV infection.

Needless to say, political will for the prevention and treatment of HCV and TB, despite their worldwide extent and deadly toll, is even weaker than it is for HIV. Worldwide, TB rates are falling too slowly, while new infections with drug-resistant TB are on the increase almost everywhere. The current infrastructure for "controlling" TB is failing for people with HIV, children, and those with drug-resistant disease. While some progress is apparent in therapeutics and diagnostics development, these advances have yet to translate into sufficiently concrete reductions in incidence, disease, or death.

There are no domestic reimbursement programs for HCV treatment, and globally—despite the recent progress in Thailand described by Karyn Kaplan in her chapter below—neither a public health– nor an individualized medical approach to HCV prevention and treatment is in place. The promise of recent progress toward all-oral direct-acting antiviral (DAA) therapy will remain unfulfilled until infrastructure is created, in the United States and globally, to treat all those in need.

It is to be hoped that the activists, implementers, policy makers, and researchers who participate in the 2012 International AIDS Conference in Washington, D.C., will raise their voices to ensure that the United States adopts more ambitious goals both for its own domestic epidemic and for the global pandemic.

Below we review in brief the promising abundance of new prevention and treatment options for HIV, HCV, and TB, which are more fully detailed in the subsequent chapters.

Executive Summary

HIV

Simon Collins provides an incisive and comprehensive overview of the currently vibrant state of antiretroviral drug development. Last year saw the approval by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) of the new non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine (Janssen's Edurant) and its inclusion in a fixed-drug combination (FDC) with Truvada (emtricitabine[FTC]/tenofovir) as Complera/Eviplera (Janssen/Gilead). This year is likely to see another new chemical entity and another FDC approved by the FDA and the EMA, in this case the second available integrase inhibitor, elvitegravir, alongside the first pharmacokinetic booster since ritonavir (and the first developed exclusively as a booster), cobicistat, co-formulated along with FTC/tenofovir disoproxil fumarate as Quad (Gilead).

Quad is noteworthy for being the first FDC to be submitted to regulatory authorities *as a fixed-dose combination* product before new drug applications for two of its individual components as single agents (i.e., elvitegravir and cobicistat) were submitted. Gilead filed Quad with the FDA on December 23, 2011, but it only filed for elvitegravir as a single drug on June 27, 2012 (and then for cobicistat the day after that). The FDA is expected to act on Quad by August 27, 2012.

As noted in table 2, a number of additional FDCs are in development from Gilead, Janssen, and ViiV Healthcare including those based on cobicistat-boosted darunavir, and the third integrase inhibitor, dolutegravir, both combined with two NtRTIs (nucleotide reverse transcriptase inhibitors).

Another noteworthy advance from 2011 is the rapid progress of GS-7340, the investigational tenofovir prodrug whose advantages include improved pharmacokinetics and cellular penetration, enabling it to be given at doses as low as 10–25 mg/day compared with the current formulation of tenofovir, tenofovir disoproxil fumarate (TDF), which is dosed at 300 mg/day.

Assuming the sponsor, Gilead, pursues tiered-pricing and voluntary licensing approaches it has followed to date, this drug provides the possibility of a much cheaper NtRTI that could replace TDF and be available at a much lower price threshold, at least in developing countries, further weakening the rationale for pursuing such desperate—and toxic—measures as 20 mg/day of stavudine.[31]

Activists and people with HIV have been protesting from South Africa[32] to India[33] against a study comparing 20 mg/day of stavudine with tenofovir, which is proposed to take place in Uganda, India, and South Africa, for at least five reasons:

1. Stavudine's long-term toxicity question at 20 mg will not be answered by this trial;
2. Stavudine is more toxic than tenofovir at 30 mg. This is not expected to be sufficiently mitigated by dose reduction as the toxicities are dose- *and* time-dependent, and for this reason it is an inferior treatment option;
3. The poor tolerability of stavudine limits therapeutic durability;
4. Stavudine's side effects detract from stavudine's savings on cost; and
5. Stavudine can compromise second-line options.

As we go to press, a detailed report on the study was just broadcast on e.tv news—the biggest television news program in South Africa—which would have been seen by millions of people. Patients with terrible lipoatrophy were interviewed and made it clear they want d4T phased out. Perhaps it is time to remind funders and researchers of the critical role of community mobilization espoused in the WHO and UNAIDS Treatment 2.0 Framework Initiative, which describes one of its goals as: "People living with HIV and key populations are fully involved in the demand creation, planning, delivery and evaluation of quality-assured, rights-based HIV care and treatment programmes in all lower/middle income countries."[34] Along with treatment activists and people with HIV around the world, who know all too well the lifelong and sometimes crippling, stigmatizing toxicities of stavudine (d4T), the authors of this report hope that funders and investigators leading the proposed study turn their attention to more relevant and less retrograde approaches to treatment optimization.

Last year's *Pipeline Report* described the past decade as a "golden age of antiretroviral drug development."[35] Here we are happy to update that report's table 1 showing the status of all antiretroviral compounds reported in TAG and i-Base pipeline reports since 2003 (see table 2, HIV Treatment Pipeline, 2003–2012, below), which shows that the success rate for new molecular entities (NMEs) and FDCs that were in phase II or beyond between 2003 and 2012—assuming imminent FDA/EMA approval for elvitegravir, cobicistat, and Quad—will be 18/63, or 28.6% (down slightly from last year's reported 14/46 or 30.4%, due principally to the addition of new candidates rather than to increased attrition)

TABLE 2. HIV Treatment Pipeline 2003–2012

Class	Drug name	Generic name	Brand name	Sponsor
NRTI	FTC	emtricitabine	Emtriva (2003)	Triangle/Gilead
NRTI	AG1549	capravirine		Agouron/Pfizer
NRTI	DAPD	amdoxovir		Gilead/Emory/RFS Pharma
NRTI	MIV-310, FLT	alovudine		Boehringer Ingelheim/Medivir/Beijing Mefuvir
NRTI	ACH-126443	elvucitabine		Achillion
NRTI	D-d4FC, DPC-817	reverset		Pharmasset/Incyte
NRTI	SPD-754, AVX-754, ATC	apricitabine		Shire BioChem/Avexa
NRTI		racivir		Pharmasset
NRTI	4'-Ed4T, OBP-601 (ex festinavir)	BMS-986001		Bristol-Myers Squibb
NRTI	CMX-157			Chimerix
NtRTI	GS-7340, PMPA			Gilead
NNRTI	TMC-125	etravirine	Intelence (2008)	Janssen (ex Tibotec)
NNRTI		calanolide A		Advanced Life Sciences/Sarawak MediChem
NNRTI	DPC-083, AI-183			Bristol-Myers Squibb
NNRTI	TMC-278	rilpivirine	Edurant (2011)	Janssen (ex Tibotec)
NNRTI	BILR-355/r BS			Boehringer Ingelheim
NNRTI	UK-453061	lersivirine		Pfizer
NNRTI			Viramune XR (2011)	Boehringer Ingelheim
NNRTI (injectable)		rilpivirine-LA		Janssen (ex Tibotec)
PI		atazanavir	Reyataz (2003)	Bristol-Myers Squibb
PI	VX-175, GW-433908	fosamprenavir	Lexiva (2003)	Vertex/GlaxoSmithKline
PI		tipranavir	Aptivus (2005)	Boehringer Ingelheim
PI	TMC-114	darunavir	Prezista (2006)	Janssen (ex Tibotec)
PI	GSK-640385	brecanavir		GlaxoSmithKline
PI	PPL-100			Ambrillia/Merck
FI	T-20	enfuvirtide	Fuzeon (2003)	Trimeris/Hoffmann-La Roche
CCR5RI	SCH-C, SCH-351125			Schering-Plough
CCR5RI	UK-427857	maraviroc	Selzentry (2007)	Pfizer
CCR5RI	SCD-D, SCH-417	vicriviroc		Schering-Plough
CCR5RI/2RI	TAK-652, TBR-652	cenicriviroc		Takeda/Tobira
InI	MK-0518	raltegravir	Isentress (2007)	Merck
InI	GS-9137, JTK-303	elvitegravir		Gilead
InI	S/GSK-1349572	dolutegravir		GlaxoSmithKline/Shionogi/ViiV
InI	GSK-1265744			GlaxoSmithKline/Shionogi
InI	GSK-1265744 (LA)	long-acting GSK-1265744		GlaxoSmithKline/Shionogi
Anti-CD4 Mab	TNX-355, Hu5A8	ibalizumab		Tanox/Biogen Idec/TaiMed
AI	PRO-542			Progenics
AI	PA-457, MPC-4326	bevirimat		Panacos/Vitex/Myriad
AI	PRO-140			Progenics
AI (gp120)	BMS-663068			Bristol-Myers Squibb
PK booster	GS-9350	cobicistat		Gilead
PK booster	SPI-251			Sequoia
PK booster	CTP-518			GlaxoSmithKline
FDC	ABC/3TC	zidovudine/lamivudine	Epzicom (2003)	GlaxoSmithKline
FDC	FTC/TDF	emtricitabine/tenofovir	Truvada (2004)	Gilead
FDC	EFV/FTC/TDF	efavirenz/emtricitabine/tenofovir	Atripla (2006)	Bristol-Myers Squibb/Gilead
FDC	RLV/FTC/TDF	rilpivirine/emtricabine/tenofovir	Complera/Eviplera (2011)	Janssen (ex Tibotec)/Gilead
FDC	EVG/COBI/FTC/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir	Quad	Gilead
FDC		elvitegravir/cobicistat/emtricitabine/GS-7340		Gilead
FDC		darunavir/cobicistat/emtricitabine/GS-7340		Janssen (ex Tibotec)/Gilead
FDC		dolutegravir/abacavir/lamivudine	572-Trii	ViiV

LEGEND: NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside RTI; PI = protease inhibitor; FI = fusion inhibitor; CCR5RI = CCR5 receptor inhibitor; CCR2RI = CCR2 receptor inhibitor; InI = integrase inhibitor; AI = attachment inhibitor; MI = maturation inhibitor; PK booster = pharmocokinetic booster; FDC = fixed-dose combination

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
	approved									
	III	III	discontinued							
	II	to Emory	to RFS II		II	II	II	discontinued		
	II					to Mefuvir				
	II	II	II	I	II					
	I	I	II	discontinued						
		I	I	I	II	II	II	discontinued		
			I	I	II	discontinued				
									II	II
										I
									II	II
	II	II	II	III	III	approved				
	II		II							
	II	discontinued								
			I	II	III	III	III	III	approved	
				I	II	discontinued				
							II	II	II	II
									approved	
										I
	approved									
	approved									
	III	III	approved							
	II	II	III	approved						
			I	II	discontinued					
				I	I	discontinued				
	approved									
	I/II	discontinued								
	I	I	II	III	approved					
		I	II	II	II	III	III	discontinued		
				I	I	I	I	I	II	II
			I/II	III	approved					
			I	II	II	III	III	III	III	submitted
							II	II	III	III
							II	II	II	II
										I
	I	I	II	II	II	II	II	II	II	
	II	discontinued								
		I	I	II	II	II	II	discontinued		
			I	I			II	discontinued		
								II	II	II
							II	III	III	submitted
								III	discontinued	
								I	I	on hold
	approved									
		approved								
				approved						
								III	approved	
								III	III	submitted
										II
										II
										III

In her synoptic update, Polly Clayden describes "a flurry of activity in pediatric antiretroviral drug development and approval," but notes that "the short-and medium-term requirements of the youngest children in resource-limited settings still badly need to be addressed," with "too many formulations and yet too few real options." There are "over 45 single agents and co-formulations" but "the market is very small, and further fragmented by different regimens across age groups and weight-band doses."

Notwithstanding this daunting complexity, the last year saw FDA approval of oral suspension formulations of darunavir for children ages 3–<5 and children ≥6 unable to swallow darunavir tablets; chewable raltegravir tablets for children 2–18 years old; oral powder and tablets of tenofovir for children 2–≤18 years old; etravirine tablets for children 6–18 years old; and last—and probably of least significance, particularly in developing countries—an oral suspension of fosamprenavir for children 4 weeks to <6 years old.

It's probably noteworthy that over the past year, the FDA has approved more drugs[36] for children than for adults.[37]

Of course, FDA approval alone is irrelevant to most of the world's HIV-positive children, who live outside the United States. Clayden calls for all stakeholders to work together to expedite development of and access to the most useful, potent, and safe drugs and combinations for children of all ages. It is critical that we shorten the time from clinical trial successes in adults to those in children (and in turn throughout the age ranges), and then from FDA/EMA approval to availability of drugs where they are most needed.

On the HIV point-of-care diagnostics front for both CD4 cell quantification and viral-load testing, we find progress since last year to be so underwhelming—in spite of a spate of sponsors' claims that this year would be an annus mirabilis of point-of-care diagnostic test validation, approval, and rollout – that we decided to include only last year's CD4 point-of-care test pipeline, viral load point-of-care pipeline, and p24 test for EID (early infant diagnosis) pipeline (tables 3 to 5) with a few barely discernible tweaks.

TABLE 3. CD4 Point-of-Care Test Pipeline

Test	Turnaround Time/ Capacity	Sample Needed	Estimated Cost (USD) Test/ Instrument	Power	Environment	Training (Layperson)
Becton Dickinson point-of-care CD4 system	2–5 minutes 25–30 samples per day	20 μL finger-stick blood; 20 μL venous blood	TBD	AC, on-board long-life battery	TBD	Less than half a day
Burnet Institute CD4 counter	40 minutes 120 samples per technician per day	40 μL finger-stick blood; can also use venous blood	$2 $1,200 (eventually $400)	Battery	TBD	Less than 120 minutes
Daktari CD4 counter	8 minutes 40–50 samples per day	20 μL finger-stick blood applied to cartridge	$8 $1,000	AC, on-board long-life rechargeable battery	Temperature: 40–370°C	Less than 90 minutes
MBio Diagnostics CD4 system	20 minutes 15–20 tests per hour/100 samples per day	10 μL finger-stick blood; can also use venous blood	TBD	Battery	TBD	Less than 90 minutes
Zyomyx CD4 test	10 minutes 40 samples per day	100 μL finger-stick blood	$8 $200	None	TBD	Less than 30 minutes

TABLE 4. Viral Load Point-of-Care Test Pipeline

Test	Turnaround Time/ Capacity	Sample Needed	Estimated Cost (USD) Test/ Instrument	Power	Environment	Training (Layperson)
Alere NAT system	30–60 minutes 10 samples per technician per day	25 μL finger-stick blood or venous blood	TBD	On-board rechargeable battery	Operating temperature: 15–40°C Humidity: <90% relative humidity	Less than half a day
EOSCAPE-HIV HIV rapid RNA assay system	50 minutes 50 samples per technician per day	100 μL finger-stick blood	$20 $10,000	AC or battery	Operating temperature: <40°C	8 hours for U.S.-high-school level
Liat analyzer	30–55 minutes 8–15 samples per technician per day	200 μL plasma or 10–50 μL finger-stick blood	TBD $25,000	AC or battery	Operating temperature: 15–30°C (59–86°F)	Less than 30 minutes
SAMBA (Simple Amplification-Based Assay)	60 minutes 4 samples per run	200 μL plasma or 100 μL finger-stick blood	TBD $2,500–5,000	AC or battery	N/A	Minimal

TABLE 5. p24 Test for Early Infant Diagnosis (EID)

Test	Turnaround Time/Capacity	Sample Needed	Estimated Cost (USD) Test/ Instrument	Power	Environment	Training (Layperson)
NWGF p24 antigen rapid lateral flow assay	40 minutes 16 samples per day	80 μL heel-stick blood	$7–15 $400–700	Battery	Operating temperature: up to 43°C Humidity: up to 100% noncondensing	Minimal

Source: Murtagh M. UNITAID HIV/AIDS.[38]

Of the four CD4 tests described last year, one (Daktari) expected commercial launch at the end of 2011, and another (Zyomyx) to be available this year.[39] Both are now commencing clinical trials this year. Burnet field trials were planned in Malawi for 2011 (now 2012 due to the change in the CD4 threshold for treatment initiation from 200 cells/mm^3 to 350 cells/mm^3). MBio continues field evaluations. The launch of a new test from Becton, Dickinson and Company (BD), using image-based counting technology, is currently expected in 2012.

Alere and Liat tests were also due to be launched in 2012 (now 2013) and still possible in 2012, respectively. SAMBA continues to be field tested with Médecins Sans Frontières (MSF). The new addition, EOSCAPE-HIV, predicts a launch in 2013.

Finally, the NWGHF p24 for EID has also bumped its predictions for clinical and field trials and launch from 2011 and 2012, to 2012 and 2013, respectively.

Meanwhile UNITAID has committed substantial new funding to implementation partners MSF and the Clinton Health Access Initiative (CHAI)[40] to establish best practices for the use of new point-of-care technologies in resource-limited settings (RLS) and to expedite access to these tests at the lowest possible price, respectively, so perhaps the predicted bumper year may not be too far away. We look forward to reporting a more bubbling pipeline next year.

Last year's lack of progress in point-of-care tests allows us, however, to expand last year's coverage of treatment optimization (see "Less of the Old—or More of the New?" 2011 *Pipeline Report*)[41] into its own chapter this year, "Retrofitting for Purpose." Clayden provides a brisk overview of all the approved and pipeline drugs that are likely to play an important role in treatment optimization—which includes extending durability and potency,

reducing toxicity to a minimum, enhancing tolerability, and reducing cost, ideally together—and concludes with three simple maxims, to wit:

1. Treatment optimization must be in the interests of people with HIV;
2. Drugs and regimens need to be designed with resource-limited settings in mind; and
3. Shorten time between full FDA/EMA approval and WHO prequalification, and FDA tentative approval and that by local regulatory agencies.

Here Clayden brings out a key message, which is that the policy and regulatory pipeline linking FDA/EMA approval, WHO prequalification, FDA tentative approval, and approval by national regulatory authorities in high-burden countries (not to mention inclusion in local guidelines and timely generic products) is becoming an increasingly urgent issue not only for HIV but for TB and, soon, for HCV as well. Nathan Geffen provides a sobering update on this regulatory emergency from South Africa.

A Regulatory Reality Check from South Africa

By Nathan Geffen*

The approval of drugs by the FDA or EMA does not automatically translate into approval or access to these drugs in places with the greatest number of patients. Older drugs with worse side-effect profiles, like stavudine, didanosine, and zidovudine, are consequently still widely used throughout sub-Saharan Africa. Newer agents like raltegravir are barely used at all.

South Africa, which has good treatment data and statistics, as well as a full-fledged regulatory authority, the Medicines Control Council (MCC), provides useful examples.

Tenofovir was approved by the FDA in 2001. It was approved by the MCC only in 2007, and then only after public pressure including demonstrations against the MCC and the drug company responsible for registering it with the agency. Tenofovir only became recommended in South Africa for the first time in the Department of Health's 2010 adult *Antiretroviral Treatment Guidelines*,[42] and was widely available in the public sector only after that. Consequently about half a million people still use stavudine as part of their first-line regimens in the South African public sector. New patients

are prescribed tenofovir, lamivudine, and either nevirapine or efavirenz. However, stock-outs of tenofovir since late 2011 until the time of this writing in mid-2012 have resulted in the Southern African HIV Clinicians Society issuing the following guidance to health workers in case of shortages: "If a patient on [tenofovir] is virologically controlled and there is a TDF shortage…[t]he patient can be safely, in the short term, switched to d4T 30 mg bd [twice daily] or AZT 300 mg."[43]

There have also been stock-outs of abacavir, a drug recommended in the pediatric guidelines. Recently, this may have been associated with the tenofovir stock-outs, i.e., adult patients had substitutions with abacavir, which in turn used up supplies intended for older children.

Despite the approval of several combination antiretroviral medicines and their availability at reasonable prices in the private sector, public-sector patients, with a few exceptions, are still dispensed single-drug pills. The monthly cost of a generic equivalent of Atripla in the private sector is about US$50. This compares to less than US$20 per month for tenofovir, lamivudine (as opposed to FTC), and efavirenz purchased separately on the public-sector tender. However, if more combination medicines were put out for bidding, their prices would likely compete with those of the three drugs bought separately.

For new agents, access is particularly unpromising. Raltegravir is available in the private sector at about US$110 per month. Etravirine is about US$100 per month. These products are unaffordable to all but a few South Africans. Private medical plans, except in a few limited cases, do not pay for these. They are unavailable for general use in the public sector. No generic versions are available. Atazanavir is not purchased on the public-sector tender, and its private-sector price is about US$12 per month more expensive than that of lopinavir/ritonavir. The private-sector price of darunavir, also not available on the public-sector tender, is more than double that of lopinavir/ritonavir, and there is only one supplier. Maraviroc is not listed in the private-sector drug list, and possibly not yet approved. (Unfortunately, the MCC does not keep an easily accessed public database of approved drugs, so this cannot be verified easily.) Rilpivirine is not approved yet. The price of fosamprenavir, at US$185 per month, renders it unaffordable to virtually everyone. But tipranavir is the most unaffordable antiretroviral, at over US$500 per patient per month in the private sector. (As far as I can tell, extended-release nevirapine is not yet available in South Africa.)[44,45]

This means that second-line and salvage-regimen options are limited for public-sector patients. Department of Health guidelines still recommend didanosine for second-line treatment to children over three who were on abacavir, lamivudine, and efavirenz in their first-line regimen. Zidovudine is recommended in the second-line regimen for patients failing tenofovir-containing regimens.

The situation in South Africa is replicated, more or less—and often less—in most sub-Saharan African countries. There are several reasons why access to new agents in developing countries lags so far behind their approval by the FDA and EMA:

- Regulatory authorities, such as the MCC, are inefficient and weak. The MCC's approval of fixed-dose combination antiretrovirals has been very slow.
- Drug companies do not prioritize getting their agents approved in developing countries, where profits are small.
- Stricter global patent protection means that generic versions of newer agents are either not available at all or their availability is very limited. Raltegravir, atazanavir, etravirine, rilpivirine, darunavir, and tipranavir are examples of this. The production processes of newer agents are often more expensive as well.
- Guidelines are infrequently updated, so new treatment advances are not taken advantage of.
- The South African Department of Health has been slow to adopt fixed-dose combination medicines despite generic production of first-line regimen combination products and their many advantages.
- Stavudine and didanosine are among the cheapest antiretrovirals, making them attractive to programs with more patients than they can afford to treat.

On the positive side, the relatively late start to antiretroviral treatment throughout Africa means that the vast majority of patients are still on first-line regimens. Tenofovir is becoming more widely available, and stavudine is slowly being phased out.

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In his extensive, reflective, and unprecedentedly upbeat overview of the diverse pipelines made up of HIV preventive therapies, immune-based and gene therapies, and research toward a cure, Richard Jefferys documents the first filing for FDA approval of any intervention to prevent sexual transmission of HIV—in this case, Gilead's filing a supplemental new drug application (SNDA) for Truvada (emtricitabine/tenofovir) to prevent HIV transmission in serodiscordant couples, among men who have sex with men, and for others at risk of sexual acquisition of HIV.

After an extensive national debate, and lopsided FDA Antiviral Drugs Advisory Committee recommendations for approval (19–3 for men who have sex with men [MSM], 19–2 for HIV-negative partners in serodiscordant couples, and 12–8 for others at risk), final FDA action is expected by September 14, 2012.

It remains unclear what FDA approval will mean in practice—though it usually leads to reimbursement by private insurers and Medicare—let alone what the implications are for RLS.

Additional studies of preexposure prophylaxis (PrEP)—including both vaginal and oral approaches—remain underway, with some novel compounds such as DAPY (formerly TMC120) entering clinical trials, as well as some drugs that have yet to find their niche, such as Pfizer/ViiV's CCR5 receptor blocker maraviroc.

HIV vaccine researchers continue their dogged, thoughtful efforts to develop effective vaccine approaches, building on the apparent—but limited—success of the prime-boost approach used in RV144, and hoping to avoid the pitfalls of the STEP adenovirus-5-based vector system. The field remains a long way from a licensed product, but continued investment will be vital to the pandemic endgame.

HIV cure research continues to enjoy increased investment and attention. Last year, the National Institute of Allergy and Infectious Diseases (NIAID) awarded $70 million over five years to three Martin Delaney Collaboratories to carry out basic and clinical cure-related research.[46] The applications must have been good, because NIAID initially planned to commit only $42.5 million for these grants.

Following an international community-driven workshop in April 2011 on clinical research issues facing HIV cure-related research,[47] the U.S. FDA and National Institutes of Health (NIH) commissioned the Forum for Collaborative HIV Research to convene an 18-month public scientific and community-

inclusive advisory process to coordinate and harmonize regulatory, scientific, community, and ethical approaches to HIV cure-related clinical trials.

This week will see the release, after two years of effort, of the International AIDS Society (IAS)-led global scientific strategy, *Towards an HIV-1 Cure*.

Achieving a globally scalable HIV cure will most likely require one or a combination of small molecules that can be taken orally over a period of weeks or months. A major difficulty in HIV cure research is measuring the HIV reservoir. Curing HIV means eliminating replication-competent HIV from the body. Current methods for detecting very low levels of HIV in the body are at the very limit of detection. It is possible that someone could be cured while still having cells that were infected with defective, non–replication competent HIV. In those cases, fragments of HIV DNA, -RNA, or proteins might still be detectable even if replicating HIV was absent from the body. It will be crucial to discover and develop better quantification tools to measure HIV at the very lowest levels of detection in order to confirm experimentally the results of cure-related clinical interventions.

Jefferys notes that few new cure-related approaches have entered the clinic since 2011.

Related research continues on cellular and gene-therapy approaches to HIV treatment as well as putative HIV therapeutic vaccines. Each of these approaches—or none—may ultimately be required to cure HIV infection from infected individuals.

HCV

The hepatitis C virus (HCV) is a virological latecomer, discovered only in 1989 (whereas TB was discovered in 1882, and HIV-1 in 1982). HCV is curable, unlike hepatitis B virus (HBV) or HIV. Until 2011, when the first two hepatitis C protease inhibitors were approved, the standard of care for HCV was pegylated interferon and ribavirin, which was poorly tolerated due to a constellation of neuropsychiatric, constitutional, and hematologic side effects, and was often ineffective. Adding a third drug has made HCV treatment more effective, but tolerability is suboptimal, and triple therapy is challenging to administer—and to endure. Fortunately, many oral drugs from different classes are in development to treat—and cure—HCV.

In this year's *Pipeline*, Tracy Swan's epic overview of the explosive therapy developments in HCV demonstrates the swift application of many of the

paradigms developed for HIV in the 1990s – combination trials, real-time virological monitoring of therapy—to HCV, with extremely promising results. Some two- or three-drug combinations of all-oral DAAs against HCV have demonstrated an unprecedented ability to cure the disease in both treatment-naive and treatment-experienced people.

For the most part, DAA combination trials have enrolled people who are easily treated. Swan notes with disfavor that there are no data from people with cirrhosis, transplant candidates and recipients, and HIV/HCV-coinfected people. Unfortunately, DAAs may not reach people who are unable to wait until they are approved. Despite increasing pressure from activists, regulators, and desperate patients and their physicians, pharmaceutical companies have refused to provide early access to DAA combinations through open-label trials or other initiatives. A critical opportunity to collect information on drug safety and efficacy—and to offer potentially lifesaving treatment to people with urgent need—is being squandered.

We hope that as a result of Swan's dauntless advocacy, current and future sponsors will take heed and expedite safe and efficient development of these new combination approaches in HIV-coinfected as well as HCV-monoinfected persons.

Swan notes that, domestically, the infrastructure and reimbursement mechanisms that will be needed to reach all the nation's HCV-infected persons do not yet exist. This grim reality may blunt the rapid return on investment on which the HCV DAA combination therapy revolution is based.

Globally, there is no public-health approach even proposed for HCV prevention, diagnosis, and treatment, although at least 160 million people are chronically infected with this virus, and many will progress to end-stage liver disease unless they are treated and cured. To address this growing need, Karyn Kaplan's chapter—focusing on HCV/HIV-coinfection treatment activism in Thailand—demonstrates how a group of HIV-positive treatment activists rooted in Thailand's drug user community and linked with treatment activists from New York were able, after a long and challenging effort, to persuade the Thai government to begin including HCV treatment as part of its universal health care plan in 2012. TAG, i-Base, and our colleagues around the world hope that other developing countries move in this direction, and that the sponsors of innovator compounds to treat and cure HCV will be made available at appropriate tiered pricing levels through voluntary licenses—and if necessary through compulsory ones—so that everyone with chronic HCV infection has access to treatment over the coming decade.

TB

Though TB is the oldest of the three pathogens against which the products discussed in this report are aimed, efforts to control it globally—let alone to eliminate it as a public health threat by the year 2050 as the global Stop TB Partnership aims to do—are faltering.

Anti-TB work is hobbled by the lack of a cheap, accurate point-of-care diagnostic test that can detect within minutes, and without electricity, a cold chain, or sophisticated laboratory equipment, all the forms of this disease, which has been with humanity since before recorded history.

As Colleen Daniels and Coco Jervis show us in their depressing overview of TB diagnostics research, the pipeline for discovering such a point-of-care test for TB is a mere trickle, one in danger of drying up completely for lack of investment and long-term commitment. After a few years during which several improvements in TB culture- and molecular testing were developed, approved by the World Health Organization (WHO), and rolled out in developing countries, there has been a relative drought. Twice in the last two years, the WHO expert panel reviewed—but did not recommend for wide-scale use—a rapid molecular test to detect extensively drug resistant (XDR) TB.

In 2010, the WHO did recommend wide scale-up of the Cepheid GeneXpert MTB/RIF test, which can detect the presence of TB and resistance to two of the most commonly used drugs—isoniazid and rifampicin—within two hours. However, the test requires trained laboratory staff, electricity, annual calibration at a facility in Toulouse, France; and the machine costs US$17,000, while currently the price per cartridge is US$17—making it inaccessible to lower-income countries and barely affordable in middle-income countries such as South Africa where the burden of TB is high, and its extent hard to detect because of the high rate of HIV coinfection. Last month, the U.S. government (including USAID and the Office of the Global AIDS Coordinator/PEPFAR), along with UNITAID and the Bill & Melinda Gates Foundation, approved a proposal to accelerate and front-load purchases of the Xpert cartridges from Cepheid, which should allow the cost-per-cartridge to come down to US$9.98 as soon as this month. It remains to be seen whether this cost reduction is sufficient to allow the test's deployment where it is most needed.

The last year saw notable advances in the TB treatment pipeline, as discussed in Erica Lessem's elegant overview. These advances included results of the first novel combination regimen study for TB (the TB Alliance's NC001 study of PA-824, moxifloxacin, and pyrazinamide, which is now going into a joint study in

both drug-sensitive and drug-resistant TB); the first compassionate use program for a new TB drug ever (Janssen's open-label compassionate use study of the diarylquinoline bedaquiline [formerly TMC207]); EMA filing of the first new TB drug and class since the 1970s (Otsuka's delamanid, formerly OPC67683); peer-reviewed publication of the phase II Otsuka study in persons with drug-resistant TB; and the establishment by a global coalition of activists of the TB Community Advisory Board (TB CAB), which has met in Washington, D.C., and in Durban, South Africa, to increase community engagement with TB research.

Finally, earlier in July 2012, Janssen (formerly Tibotec) announced its FDA filing for accelerated approval for bedaquiline (formerly known as TMC207), for the treatment of drug-resistant TB.[48] We hope that EMA and FDA actions on delamanid and bedaquiline take place with an awareness of the urgent and expanding threat posed by drug-resistant TB worldwide.

For the first time, it is possible to envisage a future in which people with all forms of TB, whatever their resistance profile, could be treated with a curative regimen made up of drugs to which the infecting organism is susceptible. This would involve a combination of new and existing compounds, or all-new drugs—if the six novel agents currently in phases I–III, or their successors, are safe and effective enough for wide use. It is still far too early to be certain of success, and unlike with HCV or HIV, there are far too few innovator compounds—or companies—yet in the clinic. Recent indications from the FDA of potential regulatory flexibility regarding endpoints for registrational studies are encouraging.

As with HIV, the TB vaccine field remains less well populated with candidates or companies, but a safe and effective vaccine against pulmonary transmission of TB will remain a requirement if the disease is ever to be eliminated. Richard Jefferys notes in his chapter on TB vaccine development in 2012 that the pipeline is not growing as fast as it needs to.

On May 30–June 1 2012, a group of activists, implementers, policy makers, and researchers, met in Cambridge, Massachusetts, to focus on how to achieve the most rapid possible reduction in new TB infections, TB deaths, and suffering and stigma caused by TB. The statement by this group on "Zero New TB Infections, Zero TB Deaths, and Zero TB Suffering," will be released this week in Washington, D.C.

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THE ANTIRETROVIRAL PIPELINE

By Simon Collins

Introduction

Two aspects of antiretroviral treatment over the last year have developed along separate paths despite their clear connection. The degree to which they are tied is easier to speculate on than to predict, and this has a new significance for HIV pipeline research.

The first—and the traditional focus for this annual pipeline review—is the mainstream development of new compounds through early and regulatory phases of development, hopefully to approval and postmarketing research.

The development pyramid rising from tens of thousands of potential molecules screened to achieve one marketed drug is well described. This report summarizes the progress of compounds that generally have results from phase II/III studies, and this year it highlights a new dynamic for the coformulated end product to become elevated, in many cases, above that of an individual new drug.

So within a couple of years, there might be half a dozen single-pill, once-daily, fixed-dose combinations (FDCs). For a doctor to be able to say, "Which one of these six pills would you like to take each day?" is a significant achievement for anyone who remembers the complexities of early HAART (handfuls of pills with multiple doses and diet restrictions)—even if, in the detail, virological failure with resistance to one FDC is likely to preclude subsequent reliance on others. Intercompany collaborations are unusual in other health areas, but traditional obstacles have been overcome by some companies for HIV formulations. The Western market for better drugs is still both highly competitive and lucrative.

However, the second strand of development, progressing just as insistently, is the funding pressure on health services, especially in countries where they are based on public health– or donor aid. During an economic recession, in both rich and poor countries, the potential impact of patent expiration on commonly used, established drugs challenges research-based companies to not only produce better, more effective, and safer drugs, but then bring them to market at a price that will enable them to be widely used.

These economic pressures already focus the concerns of health workers and activists as much as those of health care purchasers. For most people with access to treatment, HIV has become a largely manageable illness. As such, it now has to work within mainstream health budgets. When resources are limited—and by definition they always will be—the priority for access to funding must be determined by some comparative evaluation of need. Until now, the price for new drugs generally incorporated some mark-up for added value, but antiretroviral (ARV) combinations for first-line therapy have broadly operated in a similar ballpark of approximately US$10,000 per year.

The potential for generic versions of widely used drugs to undercut drug costs in developed countries may drive the need for similarly competitive pricing for newly approved drugs, at least for countries whose health care systems have the least flexibility for premium pricing. Most insurance-based sectors of the United States may be protected, but in June 2012, the AIDS Drug Assistance Program (ADAP) still had more than 2,000 people on its ARV waiting list. The U.S. patent expiry on efavirenz in 2013 may change prescribing practice for the FDC Atripla, given its prominent role as a preferred first-line drug. The U.S. patent for nevirapine expired in November 2011, and by May 2012 the FDA had approved generic formulations from ten different manufacturers.[1] The combined formulation of AZT/3TC is also now off patent, with generic versions available.

By contrast, the cost-effectiveness of treatment at today's prices might also prompt generic companies to charge high prices, even with competition. When ddI, AZT, 3TC, and most recently nevirapine came off patent, even recognizing the more limited clinical uses, generic drug prices in Western countries were only modestly reduced compared to those of brand drugs. An indication of the importance of the financial constraints of public health care systems, however, is that even these relatively small savings have been sufficient for some countries to switch patients who were previously stable on coformulated medications such as Truvada (tenofovir + FTC) or Epzicom/Kivexa (abacavir + 3TC) to either tenofovir or abacavir, plus generic 3TC, based on little difference between 3TC and FTC. Other measures to reduce drug budgets, highlighted in the opening lecture for the pharmacology workshop this year, include pressing companies for greater discounts, discontinuing the most expensive drugs, using cheaper options preferentially, and using boosted-PI monotherapy—a strategy that was initially developed, at least in part, for U.S. patients with limited health care insurance.[2] In Europe, many of these measures are already being used in Portugal, Spain, and the United Kingdom.

Fortunately, the fiscal basis of insurance-based health care systems, especially in the United States, however problematic a model for public health care, remains sufficiently strong for industry analysts to still confidently predict that HIV drug development will continue to offer lucrative returns on investment, and that future uptake of higher priced new drugs will offset the impact of generics.[3]

For anyone following pharmaceutical PR, it also presents the unnerving spectacle of some companies highlighting inadequacies of their own established drugs to promote newer compounds that are developed based on non-inferiority studies.

Summary of Progress of Pipeline Compounds

Developments for individual compounds over the last year are summarized in Table 1. These include both updates from last year's report and data on new compounds that advanced from preclinical phases of development.

Each of the compounds is then discussed in more detail.

TABLE 1. Summary of Pipeline Compounds in 2012

Agent/Class	Sponsor	Status	Comments
rilpivirine/tenofovir/FTC NNRTI+2 NRTIs FDC	Tibotec/Janssen	Approved	Approved by the FDA in August 2011 and by the EMA in September 2011
Quad boosted integrase inhibitor + Truvada FDC	Gilead	Submitted for approval	Two phase III studies comparing Quad to Atripla and atazanavir/ritonavir + Truvada presented at CROI 2012 and published in the Lancet
dolutegravir (GSK1349572) Integrase inhibitor	Shionogi/ViiV	Phase III/ Expanded access	Top-line results from one of four ongoing phase III studies have been released Non-inferior to raltegravir in treatment-naive patients
cobicistat Pharmacokinetic (PK) booster	Gilead	Phase III	See Quad, above. Ongoing studies include co-formulations with darunavir, atazanavir, and other four-drug FDCs. Submitted as separate compound in June 2012
elvitegravir Integrase inhibitor	Gilead	Phase III	See Quad, above. Other studies ongoing. Submitted as separate compound in June 2012
GS-7340 Nucleotide (tenofovir prodrug)	Gilead	Phase III	Approximate –1.7 log viral-load reduction (vs. –1.0 log with tenofovir DF) after 10 days of monotherapy Initially a 25 mg dose was selected for development, but a 10 mg dose was used in an FDC with cobicistat. Ongoing studies include, in Quad formulation, replacing tenofovir; and in the first PI-based single-tablet FDC
BMS-663068 Attachment inhibitor (gp120)	Bristol-Myers Squibb	Phase IIb	No presentations since CROI 2011. New 24-week phase II dose-finding study ongoing with raltegravir + tenofovir vs. atazanavir + ritonavir + raltegravir + tenofovir

Agent/Class	Sponsor	Status	Comments
BMS-986001 (formerly festinavir/ OBP-601) NRTI (similar to stavudine/d4T)	Bristol-Myers Squibb	Phase IIb	Dose finding 100, 200, and 400 mg once-daily compared to tenofovir, both with efavirenz + 3TC background NRTIs
lersivirine (UK-453061) NNRTI	ViiV	Phase IIb	Phase IIb 48-week results reported non-inferiority to efavirenz in treatment-naive patients. Ongoing phase II vs. etravirine. No phase III studies announced
apricitabine NRTI	Avexa	Phase II	Although a phase III study was started, it was withdrawn by Avexa due to uncertainty over financial sponsorship
cenicriviroc (TBR-652) CCR5 inhibitor (also active against CCR2)	Tobira	Phase II	Ongoing phase II study in treatment-naive patients compared to efavirenz, both with tenofovir/ FTC background NTRIs
S/GSK1265744 Integrase inhibitor	Shionogi/ GlaxoSmithKline	Phase II	Follow-up compound to dolutegravir that may have therapeutic activity at doses of 30 mg or less. Development currently focused on a monthly injection formulation
CMX157 NRTI (similar to tenofovir)	Chimerix	Phase I	No further studies over last year
ibalizumab (TMB-355; formerly TNX-355) CD4-specific humanized IgG4 monoclonal antibody	TaiMed Biologics	Phase I	Although a phase I study is listed for 2011, there have been no new results on this compound for several years
rilpivirine-LA (long-acting injection) NNRTI	Janssen	Phase I	The only study of the long-acting formulation (monthly injection) was stopped early by the sponsor. Future studies include it as a comparator to a similar formulation of S/GSK1265744

Approvals since the 2011 Report

As we went to press, only one new compound had been licensed since the last pipeline report. This was a fixed-dose combination (FDC) of the NNRTI rilpivirine coformulated with tenofovir and FTC that was approved by the U.S. Food and Drug Administration (FDA) in August 2011 (as Complera), and by the European Medicines Agency (EMA) in September 2011 (as Eviplera).[4]

Rilpivirine had already been approved in the United States a couple of months earlier. Notably, this received an indication only for the treatment-naive, with a caution to use it in patients with viral load <100,000 copies/mL and highlighting the importance of adherence, coadministration with food, and the potential for cross-resistance with both first- and second-line NNRTIs.[5]

However, several exciting compounds are on the brink of regulatory decisions, and others are in advanced phase III studies.

Update on Compounds with Phase II/III Results

The upcoming pipeline can be categorized broadly as "hopeful," "early days," and "trailing."

Hopeful: Quad (elvitegravir/cobicistat/tenofovir/FTC), elvitegravir, cobicistat, GS-7340, dolutegravir, 572-Trii (dolutegravir/abacavir/3TC), and Quad variations (using GS-7340 and darunavir).

Early days: S/GSK1265744, lersivirine (UK-453061), BMS-986001 (formerly OBP-601), BMS-663068, cenicriviroc (TBR-652), rilpivirine-LA (long-acting injection).

Trailing: apricitabine, ibalizumab (TMB-355; formerly TNX-355), CMX157, CTP-518.

Quad: Elvitegravir/Cobicistat/Tenofovir/FTC

Currently in development by Gilead, Quad is a single-tablet FDC of elvitegravir (an integrase inhibitor), cobicistat (a pharmacokinetic [PK] booster), tenofovir (a nucleotide), and FTC (a nucleoside) that is taken once daily with food. Quad was submitted to the FDA in October 2011, with a decision expected by August 2012.

Top-line results from two randomized, double-blind, placebo-controlled phase III studies were released in October 2011, presented at the 19th Conference on Retroviruses and Opportunistic Infections (CROI) in March 2012, and published in the *Lancet*. They compared Quad to efavirenz/tenofovir/FTC (Atripla) in one, and to atazanavir/ritonavir plus tenofovir/FTC in the other.[6,7]

In May 2011, the FDA Advisory Committee reviewing Quad voted 13–1 to recommended approval based on general safety and efficacy, but highlighted renal complications (the vote against was from a renal specialist, and based on lack of safety data compared to existing options). The limited data on use in women and African Americans, among whom renal disease is more prevalent, have also been noted by the FDA.[8]

The primary endpoint in both phase III studies was the proportion of patients with undetectable viral load (<50 copies/mL) at week 48 by intention-to-treat analysis, with non-inferiority defined by a lower margin of –12%, and included patient stratification by baseline viral load above and below 100,000 copies/mL. Virological efficacy was around 90% (though median baseline viral load was only 31,000 copies/mL in one study), tolerability was good, and discontinuations were notably low in all arms. Both found Quad to be non-inferior to the comparator combinations.

Study 236-0102 compared Quad to Atripla and enrolled 700 treatment-naive patients in the United States and Puerto Rico.[6]

Baseline characteristics included a mean age of 38 years and low median viral load (31,000 copies/mL), although one-third of participants started at >100,000 copies/mL. Mean CD4 count was just under 400 cells/mm^3, with 12% of participants starting below 200, 32% starting at both 200–350 and 350–500, and 23% starting at >500 (percentages for Quad arm, but similar to Atripla). The study group was largely male (88%), with ethnicity 61% white, 31% African American, and 8% other. Fewer than 5% of participants in each arm had either HBV- or HCV coinfection.

Discontinuations before week 48 occurred in 11% versus 13% in the Quad versus Atripla arms for broadly similar reasons.

Viral load was suppressed to undetectable in 88% versus 84% of patients (difference +3.6%, 95%CI, –1.6 to +8.8) meeting criteria for non-inferiority, with 7% of patients in each arm having virological failure, and 5% versus 9% having missing data (all Quad vs. Atripla, respectively). Responses by subgroup (viral load, CD4 count, race, sex, age, and adherence level) were

not significantly different, but tended to favor Quad. CD4 increases favored the Quad arm, with +239 cells/mm^3 versus +206 cells/mm^3 respectively ($P = 0.009$).

Approximately half of the patients in each arm failed with mutations associated with resistance to either integrase inhibitors (mainly E92Q) or NNRTIs (mainly K103N) in 8 out of 14 versus 8 out of 17 patients, respectively.

Most side effects were reported as mild (grade 1), with statistically significant differences including more nausea in the Quad arm (21% vs. 14%), and more abnormal dreams (15% vs. 27%), insomnia (9% vs. 14%), dizziness (7% vs. 14%), and rash (6% vs. 12 %) in the Atripla arm.

Discontinuations related to side effects occurred due to rash (0% vs. 1.4%), renal abnormalities (1.4% vs. 0%), depression (0.3% vs. 0.9%), abnormal dream (0% vs. 0.6%) in the Quad versus Atripla arms, respectively, with 3% in each arm stopping due to each of fatigue and paranoia.

The most frequent grade 3 or 4 laboratory abnormalities occurring in more than five patients in each arm were broadly similar and generally low, including creatinine kinase (5% vs. 11%), AST (2% vs. 3%), ALT (1% vs. 3%), GGT (2% vs. 5%), neutrophils (2% vs. 3%), amylase (2% in each arm), and hematuria (2% vs. 1%), all in Quad versus Atripla, respectively.

Serum creatinine increased by approximately 0.1–0.2 mg/dL by week 2 in the Quad arm that was maintained through to week 48, compared to no change with Atripla ($P < 0.001$).

Increases in fasting total cholesterol (TC), LDL cholesterol, and HDL cholesterol were significantly greater in the Atripla compared to the Quad arms, but there was no difference among groups in the more clinically significant TC/HDL ratio or in triglycerides (+7 mg/dL in each arm).

The second Quad study, called 236-0103, compared Quad to atazanavir/ritonavir, a boosted HIV protease inhibitor, plus tenofovir/FTC (Truvada) in 708 treatment-naive patients.[6] Baseline characteristics were broadly similar to the 236-0102 study: mean age 38 years, 90% male, and 74% white. CD4 count, viral load, and hepatitis coinfection were also similar, with 40% of participants having a viral load ≥100,000 copies/mL (but median was slightly higher at 63,000 copies/mL). Exclusion criteria for this study included renal function defined as eGFR <70 mL/min.

Virological efficacy (<50 copies/mL at week 48) was 92% versus 88% (difference +3.5%, 95%CI, –1.0% to +8.0%) in favor of Quad, which met the criteria for non-inferiority. In patients with baseline viral load ≥100,000 copies/mL, response rates were 85% versus 82% (P = NS). Virological failure (FDA snapshot algorithm) was 5% in both arms. Median CD4 increases in this study were similar at +207 cells/mm^3 versus +211 cells/mm^3, and discontinuation rates for side effects were 4% versus 5% (in Quad and atazanavir/r arms, respectively).

Side effects occurring in ≥5% of patients were similar in each arm, apart from elevated bilirubin levels, which were significantly higher in the atazanavir/ritonavir arm. Discontinuations occurred due to diarrhea (4% vs. 5%); pyrexia (1% vs. <1%); nausea (1% vs. 0%); vomiting and fatigue (each <1% vs. 1%); and jaundice, dizziness, ocular icterus, and drug eruption (each 0% vs. <1%). The most frequent grade 3 or 4 laboratory abnormalities occurring in at least 2% in either arm were broadly similar, including creatine kinase (6% vs. 7%); hematuria (4% vs. 2%); AST (2% vs. 3%); ALT (2% vs. 2%); amylase (2% in each arm); and increased bilirubin (1% vs. 58%), all in Quad versus atazanavir/ritonavir arms, respectively. Serum creatinine increased by approximately 0.08 mg/dL by week 2 in the Quad arm, and was 0.12 mg/dL at week 48, compared to 0.05 mg/dL with atazanavir/ritonavir (P < 0.001). Median change in CLCr from baseline was –12.7 mL/min in Quad and –9.5 mL/min (P < 0.001) in the atazanavir/ritonavir arm. Lipid increases were similar for TC, LDL, and HDL cholesterol (all P = NS), but triglycerides increased by less in the Quad arm (+5 mg/dL vs. +23 mg/dL; P = 0.006).

Median changes in bone mineral density were similar in each group. Spine changes reduced by about 3% at week 24 and remained stable, with reductions at week 48 of –2.45% versus –3.48% (P = 0.25 for between-arm comparison). Reductions at the hip were continuous slopes for both combinations of about –1.5% versus 2.0% at week 24, and –2.87% versus 3.59% at week 48 (P = 0.12).

Safety data compiled for the 206-page FDA briefing document reported renal adverse events of 1.6% for Quad (N = 12) compared to 0.5% (N = 2) for Atripla and 0.6% for atazanavir (N = 2), leading to six discontinuations in the Quad group versus one with atazanavir. Two of these patients had eGFR <70 at baseline or screening. Rates for acquired Fanconi syndrome and renal tubular disorder were reported as 0.7% and 0.3%, respectively.[8]

These results all broadly support this important new FDC option. At least three phase III studies are already ongoing for patients currently stable on PIs, NNRTIs, or other integrase-based combinations to switch to Quad.[9,10,11]

Elvitegravir (GS-9137)

Elvitegravir is a once-daily integrase inhibitor that, with boosting (150 mg cobicistat or 100 mg ritonavir), has a plasma half-life of 9.5 hours, and achieves mean viral-load reductions of approximately 2 log copies/mL after 10 days of monotherapy.[12]

Elvitegravir is metabolized primarily by CYP3A and secondarily via UGT1A1/3, and requires a reduced dose (from 150 mg to 85 mg daily) if used in combination with atazanavir. Recent studies reported no interactions with rosuvastatin, but noted that rifabutin and other mycobacterial drugs are currently contraindicated.[13,14]

Although it has already been submitted for regulatory approval as a component of Quad, and the majority of ongoing research includes Quad, elvitegravir is also included in a similar FDC from Gilead that uses the tenofovir prodrug GS-7340 in place of tenofovir.

Elvitegravir is also being developed as a separate compound, though the subject of more limited research.

A phase III randomized study is currently comparing elvitegravir/ritonavir to raltegravir (with both arms using additional drugs) in treatment-experienced patients. Now enrolled, the study should produce results shortly.[15]

Elvitegravir was submitted to the FDA as a separate compound in June 2012.[16]

Cobicistat (GS-9350)

Cobicistat is a PK booster that is a potent inhibitor of cytochrome P450 3A4. It is a weak inhibitor of 2D6 but not other CYP or UGT pathways, and has an inhibitory effect similar to ritonavir's on other transporters that affect drug metabolism, including Pgp, BCRP, and OATP1B1/3.[13,17]

Cobicistat also appears to have a short-term side-effect profile similar to that of ritonavir, including gastrointestinal and lipid effects, but without antiviral activity. Although the potential for renal complications has been raised in studies based on its use in Quad, mean eGFRs at week 24 were stable, and similar to ritonavir in a phase II study (that included tenofovir). The strategic importance of cobicistat is as a new option to develop advances in boosted formulations.[18]

Compiled renal data prepared for the Quad submission to the FDA reported similar renal events in the cobicistat versus ritonavir studies (N = 6 each), with a 1.5% discontinuation rate for cobicistat. Cobicistat also produces a small increase in serum creatinine that results in a small decrease in estimated but not actual GFR. An outstanding issue related to clinical management of increases in serum creatinine seen in both Quad studies has been proposed: an increase of 0.4 mg/dL or greater may be able to be used as a conservative cut-off to address concerns about potential tenofovir renal tubular toxicity.[8,19]

As with elvitegravir, the PK booster cobicistat has already been submitted for regulatory approval as a component of Quad. It is also coformulated in an FDC with elvitegravir, FTC, and the tenofovir prodrug GS-7340, and, in a collaboration between Gilead and Janssen, with an HIV protease inhibitor, darunavir, FTC, and GS-7340.[20,21]

There are also plans for collaborations between Gilead and Janssen (for darunavir) and BMS (for atazanavir) to combine cobicistat with these PIs to eliminate the need for a separate booster.[22,23]

Limited research is ongoing for cobicistat as a separate compound, but 48-week results are expected in 2012 from the phase II study comparing cobicistat to ritonavir as a booster for atazanavir in treatment-naive patients.[19]

Results from a recent study presented at the 13th International Pharmacology Workshop included data supporting the safety of using cobicistat twice daily (150 mg BID resulted in approximately fourfold higher exposure compared to 150 mg once daily). While the impact of cobicistat when boosting darunavir is similar to ritonavir, this is not seen with tipranavir (an HIV protease inhibitor used for multidrug resistance). Tipranavir exposure is markedly lower when boosted by cobicistat, and cobicistat exposure is 90% lower compared to cobicistat alone.[24]

Comparable bioavailability results were also presented for two fixed-dose formulations of darunavir/cobicistat (800 mg/150 mg) when compared with darunavir/ritonavir (800 mg/100 mg).[25]

Ongoing phase III studies use cobicistat in combinations that boost darunavir or atazanavir and include a safety study for patients with mild to moderate renal impairment at baseline.[26]

Cobicistat was submitted to the FDA as a separate compound in June 2012.[27]

GS-7340

GS-7340, in development by Gilead, is a prodrug of the NRTI tenofovir, but has higher potency at much lower concentrations, and will also use less active pharmaceutical ingredients (API) in relation to viral impact, something that affects the final cost significantly in resource-limited compared to Western settings. This is important given the reliance on stavudine which—despite its toxicities—is still used by perhaps 50% of people on treatment globally who have been unable to access tenofovir. The low milligram dose will also extend its use in co-formulations with other ARVs.

While tenofovir is extensively used—estimates suggest by perhaps 50% of patients in Western settings, and Gilead now markets based on "nine million patient years experience"—there remain concerns about its potential long-term impact on renal function. In 2012, two large cohort studies—the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study in Europe, and a study at the U.S. Department of Veterans Affairs—both reported associations between tenofovir use and renal health in patients with normal renal function at baseline.[28,29]

Compared to the current formulation of tenofovir, the in vitro median effective concentrations (EC50s) for GS-7340 are 0.008 uM versus 0.05 uM in MT-2 cells, 0.003 uM versus 0.015 uM in PBMCs, and 0.014 uM versus 0.06 uM in macrophages. An initial dose-finding 10-day monotherapy study with an early formulation reported viral-load reductions of about –1.0 log at 50 mg and 150 mg doses, compared to 0.5 log with TDF, with plasma concentrations of GS-7340 that were 88% lower, and intracellular concentrations fourfold higher, compared to TDF.[30]

At CROI 2012, a similar dose-finding study randomized 38 treatment-naive or -experienced (but tenofovir-sensitive) patients to 10 days GS-7340 monotherapy using 8 mg, 25 mg, and 40 mg of a new formulation, with placebo and TDF arms as controls. The primary endpoint was the time-weighed average change in viral load (DAVG) at day 11.[31]

Baseline characteristics included: age 38 years; 97% male; and 50% white/38% African American. The mean viral load and CD4 counts were 31,000 copies/mL and 478 cells/mm^3, respectively.

DAVG results were –0.76, –0.94, –1.13, –0.48, and –0.01 log copies/mL in the 8 mg, 25 mg, 40 mg, TDF, and placebo arms, respectively, with median viral-load reductions of –1.08 log (8 mg), –1.46 log (25 mg), –1.73 log

(40 mg), –0.97 log (TDF), and –0.07 log (placebo). There were significant differences between both the 25 mg and 40 mg arms when compared to TDF, but not for the 8 mg dose.

Plasma tenofovir exposures across the GS-7340 groups were approximately 80–97% lower compared to TDF, with intracellular concentrations in PBMCs sevenfold higher with the 25 mg dose, and twentyfold higher with the 40 mg dose.

There were no clinically significant laboratory abnormalities or drug-related serious adverse events, no discontinuations, and no evidence of resistance over the 10 days.

Although no renal concerns were seen after 10 days, this will be an important aspect of further studies, including whether increased intracellular concentrations of GS-7340 accumulate in renal tubule cells. In vitro data on MT-2 cells, PBMCs, and macrophages did not find increased levels of intracellular diphosphates. CNS penetration by GS-7340 is expected to be similar to TDF.

Although selection of the 25 mg dose for single compound has been reported, a pharmacokinetic interaction with cobicistat that boosts GS-7340 supported use of 10 mg doses in coformulations;[32] this includes with elvitegravir/cobicistat/FTC (Quad+), and with darunavir/cobicistat/FTC in the first PI-based single-tablet FDC,[14] both of which are currently in ongoing phase II studies.[33,34] The interaction of renal complications with the renal impact of cobicistat will also be a key aspect of these studies.

Dolutegravir

Dolutegravir is an integrase inhibitor being developed by ViiV that has advantages over raltegravir and elvitegravir. It is dosed once daily in treatment-naive patients and twice daily in treatment-experienced patients; requires no boosting; and has low PK variability, a potentially distinct resistance profile to raltegravir, and high potency at a low milligram dose.[35,36]

Dolutegravir is metabolized primarily by UGT1A1, using CYP3A as a minor route (10–15%), but it does not have a clinical impact of inducing or inhibiting major CYP, UGT, or transporter pathways (except OCT2). It is expected that interactions will be able to be clinically managed by dose adjustment, when appropriate. Currently known interactions include significantly increased dolutegravir exposure with atazanavir (boosted and unboosted), and reduced

exposure with darunavir, fosamprenavir, tipranavir, efavirenz, and rifabutin (by 30–75%; not considered clinically significant for treatment-naive patients). However, etravirine reduces dolutegravir exposure by 88%, and can be used only if coadministered with lopinavir/r or darunavir/r (which increase dolutegravir exposure). Dolutegravir needs to be given twice-daily with rifampin and antacids separated by at least two hours (due to metal cation chelation rather than a pH effect).[37]

There are encouraging safety data out to 96 weeks from phase II studies,[38] and phase III results reported non-inferior top-line results compared to raltegravir in treatment-naive patients.[39] In addition, a study with two FDC formulations of dolutegravir with abacavir and 3TC (compound name: 572-Trii) has been completed,[40] and encouraging results have already been presented for a pediatric sprinkle formulation.[41] Dolutegravir is already available in an expanded access program.[42,43,44]

In April 2012, results from the phase III SPRING-2 study comparing dolutegravir to raltegravir in treatment-naive patients reported non-inferiority based on viral suppression (<50 copies/mL) in 88% versus 85% in the dolutegravir versus raltegravir arms, respectively (95%CI, –2.2% to +7.1%), with the lower margin of the 95% confidence interval being above the prespecified –10%. No tolerability differences were noted between arms.[45]

Results from the SPRING-1 dose-finding study of dolutegravir/abacavir/3TC compared to efavirenz/tenofovir/FTC (Atripla) in treatment-naive patients were presented in a late-breaker oral session at CROI in 2012, and were broadly similar at 96 weeks to 48-week results for the 50 mg arm.[38]

Two hundred and five participants were randomized to receive dolutegravir at 10 mg, 25 mg, or 50 mg once daily compared to efavirenz. Baseline demographics included: 86% were male; 80% were white; 26% had baseline viral load >100,000 copies/mL; and 67% used tenofovir/FTC as the NRTI backbone.

At week 96, the proportion of patients with viral load <50 copies/mL (TLOVR) was 79%, 78%, and 88% in the 10 mg, 25 mg, and 50 mg arms, respectively, versus 72% in the efavirenz arm. Virological failure occurred more frequently in the lower-dose arms: in 13% (N = 7), 8% (N = 4), 4% (N = 2), and 8% (N = 4) of the 10 mg, 25 mg, 50 mg, and efavirenz arms, respectively, but these were low study numbers, and half these patients who counted as treatment failures by TLOVR analysis resuppressed to <50 copies/mL by week 96. No mutations associated with resistance to integrase inhibitors or NNRTIs were seen in these patients.

CD4 count increases were not statistically different at week 96: +338 cells/mm^3 for the combined dolutegravir arms versus +301 cells/mm^3 for efavirenz ($P = 0.155$).

Only two people discontinued dolutegravir due to side effects (one in each of the 25 mg and 50 mg arms) compared to five in the efavirenz group. Side effects were lower in the dolutegravir arms, although serious side effects were similar. The only grade 3/4 lab abnormalities were single cases of ALT elevation associated with acute hepatitis C. No differences in renal markers were observed between the two groups.

There are ongoing phase III studies of dolutegravir in treatment-experienced patients with resistance to raltegravir or elvitegravir, and to darunavir/ritonavir in treatment-naive patients.[45,46,47,48]

Results from research in treatment-experienced patients with mutations associated with virological failure after using other integrase inhibitors have been encouraging, after the adoption of an increased dose (to 50 mg twice daily), given the historical difficulties of within-class resistance.[49,50]

The expanded access program for dolutegravir is already open in Europe and the United States, although with a caution on the importance of using it in combination with other active drugs in order to avoid early resistance and further loss of treatment options in patients with complicated multidrug resistance.[42,43,44]

S/GSK1265744

While the focus on dolutegravir generated considerable excitement, there is also interest (though minimal data) on the follow-up integrase compound at GSK/ViiV called S/GSK1265744, which has a longer half-life (approximately 30 hours vs. 15 hours for dolutegravir).

The early phase I/II results presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in 2009 reported a median viral-load reduction of 2.6 log copies/mL following 10-day monotherapy at a 30 mg once-daily dose in treatment-naive patients, with discussion that a lower milligram dose may also be possible.[51]

A long-lasting injection formulation is also being investigated to compare its pharmacological properties to those of both oral administration and the long-acting formulation of the NNRTI rilpivirine, with potential use as both treatment and preexposure prophylaxis (PrEP).[52,53]

Update of Other Compounds

Lersivirine

Lersivirine (previously called UK-453061) is a once-daily NNRTI owned by ViiV that was originally developed by Pfizer, and that has a resistance pathway at V108I that appears distinct from the K103N or Y181C pathways associated with first-generation NNRTIs.

The latest data come from a phase II double-blind, placebo-controlled study that randomized 193 patients (1:1:1) to either 500 mg or 750 mg of lersivirine or to standard-dose efavirenz, each with once-daily tenofovir/FTC. The primary endpoint was the percentage of patients with viral load reduced to <50 copies/mL at 48 weeks, with follow-up out to 96 weeks (by ITT missing = failure analysis).[54]

Baseline CD4 count and viral load were median 310 cells/mm^3 (range 122–955) and mean 50,000 copies/mL (range 1,500–1,600,000), respectively. Approximately 35% of patients had baseline viral load >100,000 copies/mL, and this was reflected in prespecified analysis of the results.

Other baseline characteristics included: mean age 36 years (range 21–62); 27% female; and 60% white/30% black/10% other. While the majority of people had subtype B, approximately 30% of people had subtype C related to patients at South African sites.

At week 48, the percentage of patients with viral load <50 copies/mL was 79%, 79%, and 86% in the 500 mg, 750 mg, and efavirenz groups, respectively. Although the study was not powered to detect a difference in efficacy among arms, the lersivirine arms suggested a poorer response compared to efavirenz (500 mg: –9% difference; 80%CI, –18.1, 0.8; and 750 mg: –8% difference; 80%CI, –17.0, 1.2).

Results stratified by baseline viral load (which was lower in the >100,000 copies/mL group) or geographical region (which was lower for sites in South Africa) did not contradict this finding. Mean CD4 count increased approximately +190 cells/mm^3 from baseline and was similar.

Limited data on virological failure (in 4, 5, and 3 patients in the 500 mg, 750 mg, and efavirenz groups, respectively) indicated that the lersivirine arms were associated with M184V plus NNRTI mutations when resistance was isolated. The one person with identifiable mutations in the efavirenz arm failed with K103N alone.

Overall, the combined safety analysis reported a similar incidence of side effects in each group, but fewer grade 3/4 events in the lersivirine groups (N = 2 and 3) compared to efavirenz (N = 8). Laboratory abnormalities were infrequent and evenly distributed among arms. Lipids were broadly stable for lersivirine compared to increases in TC, LDL, HDL, and triglycerides (TG) for efavirenz, but this resulted in little difference between the lersivirine and efavirenz groups (+0.24 and –0.06 vs. –0.3) in the change in the TC:HDL ratio, which is used to evaluate cardiovascular risk.

However, the study concluded that both lersivirine doses showed similar efficacy to efavirenz over 48 weeks in treatment-naive patients and had different side effect profiles compared with efavirenz.

While there is still a role for a new NNRTI with activity against nevirapine- and efavirenz-associated resistance, the higher reports of nausea and headache, even if low grade, might explain why no further clinical research is ongoing other than follow-up of patients in the initial studies.[55]

BMS-986001 (NRTI)

BMS-986001 (previously OBP-601 and, briefly, festinavir) is an NRTI with a structure similar to that of stavudine (d4T), but a safety profile that is unlikely to be associated with similar side effects. In vitro studies suggest that BMS-988001 is a weak inhibitor of DNA synthesis, and unlikely to affect mitochondrial function.

The most recent data, first reported in 2010, come from a revised analysis of the phase I/II dose-finding study in treatment-experienced patients (off treatment for at least three months). Following 10 days of monotherapy, median reductions in viral load on day 11 were 0.97, 1.15, 1.28, and 1.15 log in the 100, 200, 300, and 600 mg groups, respectively (vs. –0.07 in the placebo group), from median baseline levels across groups of 4.3–4.6 log (range 3.5–5.3 for the whole study).[56]

In vitro data on the drug susceptibility of BMS-986001, including susceptibility to the Q151M NRTI multidrug-resistant mutation, were presented in a poster at CROI in 2008. Although antiviral activity was reduced in the presence of most viruses carrying nucleoside-associated mutations (5- to 10-fold), including M41L (0.3- to 4.3-fold) and D67N (1.6- to 7.8-fold) resistance mutations, together with K103N with or without M184V. Viruses carrying the Q151M mutation were mildly hypersusceptible to BMS-986001 (0.1- to 0.2- fold), even in the presence of K65R (0.3- to 1.3-fold).

A new 48-week phase II dose-finding study is comparing once-daily doses of 100, 200, and 400 mg plus efavirenz and 3TC to a control arm of efavirenz, tenofovir, and 3TC.[57]

BMS-663068 (Attachment Inhibitor)

BMS-663038 is a gp-120 attachment inhibitor being developed by Bristol-Myers Squibb.

Although no new studies have been presented since CROI 2011,[58,59] new studies are listed as enrolling.[60,61] These include a 24-week phase II dose-finding study with BMS-663038 dosed at 400 mg or 800 mg twice daily, or 600 mg or 120 mg once daily in combination with raltegravir and tenofovir and compared to a four-drug combination of boosted atazanavir plus raltegravir and tenofovir. The initial dose-finding study used various once- and twice-daily doses with and without ritonavir.

Cenicriviroc

Cenicriviroc (previously TBR-652) is an oral CCR5 inhibitor being developed by Tobira that has a PK profile that allows once-daily dosing, but requires coadministration with food. Cenicriviroc is also active against CCR2, which plays a role in the inflammatory and metabolic pathways, the clinical implications of which are unclear, but may include a potential benefit in future studies.

In 2010, results from an initial phase II dose-finding study reported viral-load reductions of 1.4–1.8 log with 50–150 mg.[62]

This year at CROI, interim PK data were presented for the first 25 patients enrolled (24 men, 1 woman) in a more recent 48-week phase II randomized dose-finding study of 100 mg and 200 mg doses using a new 50 mg formulation, with efavirenz as a control and tenofovir/FTC as background NRTIs for all groups. Preliminary results reported dose-proportional pharmacokinetics with average plasma concentrations between 55.6 ng/mL and 722 ng/mL (estimated IC50 is 13.1 ng/mL) and mean (CV%) Cmin values of 41.0 (64.8%) and 89.2 (59.3%) ng/mL for the 100 mg and 200 mg doses, respectively (based on trough at day 28 for 18 patients). Two patients withdrew due to protocol noncompliance and two due to tolerability, all prior to day 14. This study is still ongoing, and virological efficacy and safety data are still to be reported. Based on these results, the study will enroll the remaining 125 patients.[63]

Rilpivirine Long-Acting (LA) Formulation

The development of a nanosuspension formulation of the NNRTI rilpivirine that could be given by intramuscular injection was reported several years ago. A single-dose PK study in HIV-negative people presented at CROI this year reported prolonged exposure in plasma, genital, and rectal compartments, following single doses of 300, 600, or 1,200 mg.[64]

While rilpivirine-LA was highlighted for its potential to reduce reliance on daily adherence in the context of PrEP, it might present important options for HIV treatment as well; this would require other ARVs with a similar formulation to construct a combination. The lack of negative drug interactions between rilpivirine and raltegravir (also presented at CROI),[65] and the development of a similar formulation for S/GSK 1265744, are clearly of interest.[53]

A safety issue for long-acting formulations, especially in the absence of an antidote to rapidly eliminate the active compound in the event of a severe adverse reaction, might be covered by a period of oral dosing to confirm individual tolerability, especially as both integrase and NNRTI classes have been associated with hypersensitivity reactions.

A recent survey of 400 HIV-positive patients attending two U.S. clinics reported 61%, 72%, and 84% interest in ART injections based on weekly, biweekly, and monthly formulations, respectively, with higher interest in people with concerns about adherence, although 35% were also concerned about needle use.[66]

Apricitabine

Apricitabine is an NRTI that has been included in the previous two Pipeline reports largely on the basis of interesting phase IIb results from 2008, and the commitment, from the small Australian biotech company Avexa, that itself acquired development rights from Shire, to expand treatment options for people with multidrug resistance.

The compound is a cytidine analogue, similar to 3TC, that is dosed twice daily, with phase II results showing activity against M184V resistance, independent of the presence other nucleoside analogue mutations (TAM pathways, L74V, etc.), and also showing viral-load reductions of –0.7 log for people with three or more thymidine analogue mutations (TAMs).[67]

Theoretically, using several similar compounds with modest viral activity that could overcome aspects of drug resistance might still have a therapeutic role

for people who have run though other options. Unfortunately, the regulatory complications of developing multiple experimental options have never been resolved.

Planned phase II/III studies have been stopped or withdrawn, and Avexa is still looking for financial partners to take development forward.[68] Avexa also has integrase molecules in preclinical development.

Ibalizumab

Ibalizumab (previously TMB-355 and TNX-355) is a monoclonal antibody now owned by TaiMed that was listed as in phase I studies in the first TAG Pipeline report in 2003. While a new phase I study is listed as open to enroll treatment-experienced patients (a phase II was completed in between), it is probably reasonable to say that optimistic predictions for a breakthrough in the next year are, conservatively, likely to be slim.[69]

CMX157 and CTP-518

Over the last year, there have been no further updates on CMX157, an NRTI similar to tenofovir that reported interesting phase I efficacy data two years ago, or on the atazanavir-like protease inhibitor CTP-518 that was acquired by GSK for preclinical development in 2009.

Outlook for Fixed-Dose Combinations

The optimistic outlook for fixed-dose combinations is summarized in Table 2.

With several combinations either already approved or in phase III development, the benefits to patient care from company collaboration are clearly an example that would help in other medical fields. The market is forcing Western companies to learn from generics: fixed-dose combinations simplified treatment for patients in developing countries with numerous formulations that have never been available when patents restricted this access.

The success of Atripla is well established, but also based on the efficacy of the three individual drugs it contains. Clearly, this will be just as important for future FDCs.

The potential for protease inhibitors to be coformulated with a PK booster is important, but requires companies to collaborate. Although ritonavir was originally approved in 1996, it was subsequently coformulated with Abbott's own lopinavir in 2005, but Abbott did not license a stand-alone version until 2010, and has not coformulated it with protease inhibitors from other manufacturers that depend on boosting to reach therapeutic doses.

It is therefore helpful that agreements to co-formulate cobicistat with atazanavir and darunavir have been announced.[22,23]

TABLE 2. Approved and Pipeline FDCs and Collaborations for Joint Formulations by Brand Manufacturer(s)

Agents	Sponsor(s)	Status
Fixed-dose combinations		
AZT/3TC/abacavir (Trizivir)	GSK	Triple-NRTI combination. Approved 2000. Now rarely used
efavirenz/tenofovir/emtricitabine (Atripla)	Gilead/BMS	Approved 2006. Widely recommended and used since then
rilpivirine/tenofovir/emtricitabine (Complera/Eviplera)	Gilead/Janssen	Approved 2011
elvitegravir/cobicistat/emtricitabine/tenofovir (Quad)	Gilead	Submitted for approval; expected 2012
elvitegravir/cobicistat/emtricitabine/GS-7340	Gilead	Phase II
darunavir/cobicistat/emtricitabine/GS-7340 (PI-based FDC)	Gilead/Janssen	Phase II
dolutegravir/abacavir/3TC (572-Trii)	ViiV (GSK)	Phase III
PI + booster formulations		
darunavir + cobicistat	Tibotec (Janssen)/Gilead	Bioavailability results similar to those of darunavir/ritonavir have already been reported for two formulations
atazanavir + cobicistat	BMS/Gilead	No further information

New Compounds of Interest

Although Gilead publicized its license of non-catalytic site integrase inhibitors (NCINIs) last year from Boehringer Ingelheim, including a lead compound BI 224436, the phase 1a dose-escalation study in HIV-negative volunteers has since been withdrawn.

Peptides that work similarly to integrase-like compounds (LEDGINs), while intriguing, are still in preclinical development.[70,71]

Nanoformulations of existing ARVs still hold the same promise as they did in previous years' reports—principally achieving higher targeted drug levels using compounds that require less API. For the most part, however, interesting compounds still remain in preclinical stages of development, though some proof-of-concept studies in humans are hoped for this year.

Cellular Transcription Factors

The potential for new targets is still a focus for earlier stages of drug development, and last year's Pipeline briefly mentioned modification of antiviral human proteins including APOBEC3G, TRIM5-alpha, and tetherin that are active against HIV, but are neutralized by accessory HIV viral proteins.

Compounds that target HIV capsid include Tat inhibitors, RNase H inhibitors, gold-based compounds, tetherin (the protein that holds the virus to the host cell), and RN-18 (a compound that inhibits Vif and increases ABOBEC3G), and are still in preclinical studies.[72,73]

Research on these compounds is closely connected to some of the strategies for cure research described by Richard Jefferys in another chapter of this publication, in the role that new drugs could play if designed to target reservoirs that are currently not reached by current ART. The existence of such sanctuary sites, while controversial, is clearly plausible, and supported by some research groups (though not by others).

In addition to designing drugs to target specific reservoirs, a study at CROI this year reported on the potential of APOBEC3G to intensify the impact of raltegravir.[74]

Conclusion

While in the last year only one new ARV compound was approved, several new compounds and FDCs are reaching regulatory stages, and this is expected to change treatment options, though this will also be dependent on how these drugs are priced in different markets.

It also remains to be seen whether the promising results reported in clinical trials, some of them involving less advanced patients, can be matched in routine or real-life settings, where patient characteristics are often very different.

These new drugs, while developed for a treatment-naive indication, also have promising activity for people with drug resistance, although some potentially useful compounds for resistant patients are still shelved waiting partnership with larger companies.

The potential development of treatments that work with human transcription factors and other cellular mechanisms still appears promising.

Finally, the industry outlook on new drugs, even at costs similar to or higher than those of current drugs, is sufficiently strong to ensure continued research in the near future. This is important. Current drugs are far from perfect, and an HIV cure, even if achievable, is optimistically suggested to be 10 to 20 years away.

Access to new treatments in anything other than the most financially wealthy settings (including some European countries) is less stable or certain, however, and this may result in further dividing treatment options in Western countries.

This might lead to a situation where pipeline compounds with very low milligram doses have the potential to become more widely used in developing rather than developed countries (depending on pricing policies for resource-limited settings) if the same manufacturers decide on premium pricing for new drugs for a Western market.

Sources

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THE PEDIATRIC ANTIRETROVIRAL PIPELINE

By Polly Clayden

In the past year—since our last *Pipeline Report*—there has been a flurry of activity in pediatric antiretroviral drug development and approval.

While overall the pipeline for children looks encouraging, the short- and medium-term requirements of the youngest children in resource-limited settings still badly need to be addressed. What is currently available to treat them has been described as, "too many formulations and yet too few real options."[1] At present, national programs use over 45 single agents and co-formulations due to an initial requirement by many programs to use single innovator formulations. Meanwhile the market is very small, and further fragmented by different regimens across age groups and weight-band doses. As a result, orders are always low-volume, and this threatens both access and the sustainability of the market. Therefore, the focus needs to be on a smaller number of products that offer the best options for children.

Several of the pipeline compounds might offer advantages over currently available options, and work is ongoing to make formulations of already approved drugs that are more suitable. For children less than three years old particularly, promising public-private partnerships may help to deliver appropriate drugs and regimens.

New Approvals

Over the past few months, we have seen the following approvals of new drugs from innovator companies by the United States Food and Drug Administration (FDA):

- On December 16, 2011, a 100 mg/mL oral suspension formulation of darunavir, and dosing recommendations for children 3 to less than 6 years of age (and children 6 and older who are unable to swallow darunavir tablets).[2] There is a waiver for children under 3, due to very high darunavir concentrations in animals (of an analogous age) and, in turn, toxicities in preclinical studies.

- On December 21, 2011, a 100 mg scored chewable tablet and a 25 mg chewable tablet of raltegravir, and dosing recommendations for children 2 to 18 years of age and weighing at least 10 kg.[3] Studies with a new granule formulation for very young children are under way.

- On January 18, 2012, an oral powder (40 mg per 1 gram of oral powder) formulation, and 150 mg, 200 mg, and 250 mg tablets of tenofovir, and dosing recommendations for children 2 to less than 18 years of age.[4]

- On March 26, 2012, a scored 25 mg etravirine tablet, and dosing recommendations for treatment-experienced children 6 to 18 years of age and weighing at least 16 kg.[5] Studies in the younger age groups are planned. Etravirine might also be a useful second-line non-nucleoside reverse transcriptase inhibitor (NNRTI) option for children as its resistance profile is different from those of nevirapine and efavirenz; it should not, however, be co-administered with rifampicin.

- On April 27, 2012, an oral suspension of fosamprenavir was approved for use in children 4 weeks to less than 6 years of age.[6] It is not expected to be used widely in young children.

These approvals by the FDA are welcome, and kick off the painstaking process that will eventually lead to access for children in the regions that need them the most. The execution of this will require commitment from many entities including the World Health Organization (WHO); national departments of health; local regulatory agencies; innovator and generic manufacturers; UNITAID and other donors; and non-governmental agencies (NGOs) such as the Clinton Health Access Initiative (CHAI), Drugs for Neglected Diseases initiative (DND*i*), and Médecins Sans Frontières (MSF).

Darunavir

Boosted darunavir is generally considered to be the most durable protease inhibitor (PI) for adults. It is increasingly used in children and adolescents in industrialized countries, particularly in those with treatment experience.[7] Boosted darunavir could be a useful option for third-line regimens for children, and for second-line regimens where boosted lopinavir has been used as first-line.

The Pediatric Antiretroviral Group of the WHO considers darunavir to be of high priority, and the 2011 Updated List of Missing Drug Formulations lists a tablet or sprinkle formulation of darunavir/ritonavir as urgently needed.[8]

However, using boosted darunavir with currently approved doses does not lend itself to harmonized, simplified weight-band dosing or to appropriate use in combined tablets to facilitate this. The establishment of a single ratio at best, or at least a simpler dosing range would make wider use of darunavir

more feasible. As the varied ratios were because of the limits of ritonavir formulations, there seems no reason why a 6:1 ratio twice daily, as for adults, shouldn't be possible. See Table 1.

TABLE 1. Darunavir/Ritonavir Dosing Recommendations for Children >3 Years Old

Weight Band (kg)	Darunavir/Ritonavir Dose mg (mL)
≥10 to <11	200 (2.0)/32 (0.4)
≥11 to <12	220 (2.2)/32 (0.4)
≥12 to <13	240 (2.4)/40 (0.4)
≥13 to <14	260 (2.6)/40 (0.4)
≥14 to <15	260 (2.8)/48 (0.6)
≥15 to <30	375 (3.8)/50 (0.6)
≥30 to <40	450 (4.6)/60 (7.5)
≥40	600 (6.0)/100 (1.25)

Children <15 kg: oral suspension, and >15 kg: reduced-strength tablets (150 mg and 75 mg)/oral suspension if they cannot swallow tablets

Raltegravir

Raltegravir's approval ushers in a new therapeutic class—integrase inhibitors—for young children that might offer some advantages over the currently available drugs. Granule formulations are more desirable for resource-limited settings as they are easier to use, transport, and store than suspensions, but still not nearly as convenient as scored, reduced-strength tablets. Alongside darunavir, raltegravir has also been suggested as a future option for third-line treatment and a high priority for children. But alongside darunavir, it is currently very expensive, with no generic options yet—even for adults.

Tenofovir

Tenofovir approval for children has been a long time coming; the FDA approved it for adults in 2001. Tenofovir is currently the preferred nucleoside reverse transcriptase inhibitor (NRTI)/nucleotide reverse transcriptase inhibitor (NtRTI) for adults in U.S., European and WHO guidelines. Both problems with a suitable formulation and concerns about toxicities have delayed its pediatric approval.

The original liquid-suspension formulation developed for children was too bitter-tasting for further development. Although the newly approved powder for younger children is an improvement, its unpleasant taste is not well masked, and it is difficult to administer and hinders adherence. Reduced-strength tablets appear to be more palatable, although exposure can be variable with the approved dose.[9]

The innovator company Gilead has experience working with generic manufacturers to produce lower-cost tenofovir, including as part of fixed-dose combinations (FDCs). It may be possible to produce pediatric FDCs or suitable formulations of scored adult tablets of tenofovir/3TC/efavirenz so that first-line treatment of children over 3 years old could be aligned with that of adults. Tenofovir given in this combination achieved exposure in children 3 years and older, dosed according to WHO weight-band tables, comparable to that in adults.[10]

However, remaining uncertainties over tenofovir-associated decreased bone mineral density have been a regulatory hurdle. There have been concerns about this in growing children and adolescents. Renal tubule dysfunction and glomerular toxicity do not appear to differ between children and adults.

Although the FDA approved it, the European Medicines Agency (EMA) initially rejected tenofovir for the 12-to-18-year age group due to concerns about poor efficacy (shown in the studies presented) and concerns about long-term bone toxicity. The agency agreed to a pediatric investigation plan both for the single agent and the investigational tenofovir-containing FDC (subject to more information on individual drugs). The decision from this agency is still pending.[11,12]

Tenofovir has long been considered a high priority for children in resource-limited settings, particularly with respect to harmonization with adult treatment. In addition, the cost of abacavir is too high, zidovudine is associated with anemia and, not least, stavudine-related toxicity in children appears similar to that seen in adults.[13,14]

The WHO has recently published a technical update on use of tenofovir in children,[15] including review of published manuscripts and unpublished data from the innovator company. If the WHO recommends its use in children over two, it would be possible for programs to align first-line treatment from three years old to adulthood.

Targeting the Youngest Children

Less than half of FDA-approved adult antiretrovirals are approved for neonates and infants. See Table 2.

WHO and national guidelines recommend universal treatment for infants and children up to two years old.[16] Conventional drug development does not always serve this population well, even with considerable incentives from the regulatory agencies.

TABLE 2. Pediatric FDA Antiretroviral Approvals by Age Group (Years)

0–2	2–6	6–12	12–18	Adults
				maraviroc
				enfuvirtide
				raltegravir
				saquinavir
			maraviroc (>16)	indinavir
			enfuvirtide	atazanavir
		enfuvirtide	raltegravir	darunavir
		raltegravir	atazanavir	nelfinavir
	raltegravir	atazanavir	darunavir	fosamprenavir
	darunavir (>3)	darunavir	nelfinavir	ritonavir
	tipranavir	nelfinavir	fosamprenavir	lopinavir
	nelfinavir	fosamprenavir	ritonavir	rilpivirine
	fosamprenavir	ritonavir	lopinavir	delavidine
	ritonavir	lopinavir	delavidine (>16)	etravirine
fosamprenavir	lopinavir	etravirine	etravirine	efavirenz
ritonavir	efavirenz	efavirenz	efavirenz	nevirapine
lopinavir	nevirapine	nevirapine	nevirapine	tenofovir
nevirapine	tenofovir	tenofovir	tenofovir	zalcitabine
zidovudine	zidovudine	zidovudine	zidovudine	zidovudine
stavudine	stavudine	stavudine	stavudine	stavudine
lamivudine	lamivudine	lamivudine	lamivudine	lamivudine
emtricitabine	emtricitabine	emtricitabine	emtricitabine	emtricitabine
didanosine	didanosine	didanosine	didanosine	didanosine
abacavir	abacavir	abacavir	abacavir	abacavir

New agents are studied in children in de-escalating age bands (but this needs to be challenged), and appropriate formulations are not always easy to develop—it can require formulating often quite big and/or insoluble molecules into appropriate forms—so even if an indication for those less than two years old is eventually approved, the process can take several years and, strictly speaking, the indication for several antiretrovirals is not from birth, but 2 to 4 weeks (and abacavir is from 12 weeks).

Traditionally, liquid formulations were developed for this age group. These are expensive, have short shelf lives, and are hard to store and transport.[17] Some of the early pediatric programs in resource-limited settings used divided adult FDCs to treat children, which can be effective in older children but can lead to inexact dosing in younger ones, who also require different ratios of some drugs in FDCs.[18]

First FDCs for Children

In order to address this, Cipla developed reduced-strength, dispersible, scored FDC tablets of nevirapine/stavudine/lamivudine (Triomune Baby and Junior) with ratios of drugs appropriate for young children and doses appropriate for WHO weight-band dosing, which were FDA-approved and accepted for WHO prequalification in 2008.[19] These formulations made it possible for programs to begin treating children in places where liquids posed too many problems.

For infants who have been exposed to NNRTIs to prevent vertical transmission, WHO and national guidelines recommend a protease inhibitor. Data from The IMPAACT P1060 trial—which showed about 20% higher rates of failure in children ages two months to three years who received NNRTI-based regimens compared to PI-based, whether or not they had been NNRTI-exposed—suggest that this recommendation might be made for all children less than two years in the next guideline revisions.[20,21] There is some concern with these results though as the trial followed children for only 24 weeks, and lopinavir/ritonavir is unpalatable in its current formulation. Nevirapine is currently more widely used in children less than two in resource-limited settings.

New Formulation of Lopinavir/Ritonavir

Cipla is working with the Children with HIV in Africa – Pharmacokinetics and Adherence of Simple Antiretroviral Regimens (CHAPAS) group at the Medical Research Council Clinical Trials Unit, the Joint Clinical Research Centre, and Baylor International Pediatric AIDS Initiative (BIPAI) Uganda to produce a more acceptable new formulation of lopinavir/ritonavir.The initial results

of the CHAPAS-2 trial on pharmacokinetics and acceptability of sprinkles in babies less than one year old and children aged four and above, funded by the Monument Trust in the United Kingdom, show comparable exposure to lopinavir/ritonavir from sprinkles to syrup in infants; it was lower than tablets in older children. The caregivers found the sprinkles were more acceptable for infants but not for older children, mainly due to the taste.[22]

Drugs for Neglected Diseases Initiative (DND*i*)

Last year, DND*i* entered the pediatric HIV arena.[23,24] DND*i* is a not-for-profit research and development organization that develops new drugs for neglected diseases such as human African trypanosomiasis, visceral leishmaniasis, Chagas disease, and malaria. DND*i* was asked by various organizations, including MSF and UNITAID, to turn its expertise to pediatric antiretrovirals for children less than three years old. In consultation with experts, DND*i* developed "ideal" and "acceptable" specifications for desired formulations or regimens (see Table 3) alongside priorities for appropriate research to facilitate their approval.

TABLE 3. Target Product Profile (TPP) for Children Less than 3 Years Old

Profile	Ideal	Acceptable
Target population	Both NNRTI-exposed and -unexposed children less than three years old	
Dosing frequency	Once daily	Twice daily
Formulation	Water-soluble, dispersible tablet that can be used with a small amount of liquid	Sprinkles or crushable pills used in food
Pill burden	One scored pill usable across broad weight bands	If two pills, must be same tablet count (or fraction) for both
Durability	High generic barrier, long half-life	
Efficacy	Same as adults	
Safety/tolerability	Well tolerated, and no lab monitoring needed	No lab monitoring needed
Palatability	No taste or nice taste	Palatable
Drug-drug interaction (DDI) with TB drugs	No DDI with TB drugs—particularly rifampicin/rifabutin	DDIs, but overcome with simple dose adjustment
Stability	No cold chain, minimum two years shelf life at room temperature	
Cost	US$50 per patient year or less (consistent with adults)	To be investigated

DND*i* is currently working on the development of a regimen of granule formulations in sachets using ritonavir-boosted lopinavir and two NRTIs. For infants receiving concomitant treatment for tuberculosis, an additional dose of ritonavir can be added; this is to overcome the drug-drug interaction between rifampicin and lopinavir/ritonavir—rifampicin dramatically reduces plasma lopinavir/ritonavir concentrations coformulated in a 4:1 ratio.[25]

They are also supporting the one-to-four-year-old cohort of CHAPAS-2.

Their plan is to have the new regimen by 2015 and to consolidate rather than further fragment the market—that is, to have this regimen replace some of the many existing formulations currently available for infants and young children.

An Innovator Company Enters the (It Would Be Nice to Say) Fray

A recent announcement of a novel public-private partnership of ViiV Healthcare, CHAI, and the Indian generic company Mylan Inc. also offers a new model that could deliver a suitable product for young children.[26]

For this initiative, CHAI has identified the ideal characteristics of a pediatric formulation of two backbone NRTIs. ViiV will oversee and fund the development of a dispersible tablet formulation of abacavir/lamivudine. Then the company will transfer the technology and resources to Mylan for production, registration, and distribution at the lowest possible cost for low-income, least-developed countries.

The tablet will be dosed according to weight, thus it will be one tablet, two tablets, three tablets, or four tablets, with four being the highest for the largest body-weight required before an infant can use an oral tablet. The dosing is being confirmed through bioequivalence studies.

Although there are already combination products with these two drugs for children, dispersible tablets are most useful.

This new formulation tastes of strawberries and is suitable for children from 12 weeks old.

Filing with the FDA is planned for July 2013 and approval expected in early 2014.

THE PIPELINE

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Etravirine

The recommended dose per weight band for children and adolescents ages 6 to 17 is based on 5.2 mg/kg twice daily. The FDA recently approved dosing recommendations for etravirine for treatment-experienced pediatric patients 6 to 18 years of age and weighing at least 16 kg as well as the scored 25 mg tablet.[5]

IMPAACT P1090 will evaluate the drug in treatment-naive and -experienced children ages 2 months to 6 years.[27]

Rilpivirine

The PAINT trial is currently recruiting treatment-naive adolescents ages 12 to18, weighing more than 32 kg, and receiving 25 mg once daily plus two nucleoside reverse transcriptase inhibitors (NrTIs). The trial will evaluate steady-state pharmacokinetics and short-term antiviral activity in this age group.[28]

TMC278-C220 is an open-label single-arm trial using the granule formulation, planned in children ages 2 to 12 years. This trial is taking a staggered approach and will study the drug in de-escalated age groups, down to 2 years of age.

Protease Inhibitors (PIs)

Atazanavir

The capsule formulation is approved in the United States for children ages 6 years and older who are treatment-naive and weigh 15 kg or more, and for treatment-experienced children weighing 25 kg or more. In the European Union, it is approved for both treatment-naive and treatment-experienced children ages 6 years and older and weighing 15 kg or more.

Treatment-naive and -experienced children ages 3 months to 6 years receiving atazanavir unboosted and boosted with ritonavir are being studied in PRINCE 1 and 2 and IMPAACT P1020A.[29,30,31] PRINCE 1 is now fully enrolled, and data are expected in early 2013; PRINCE 2 is 50% enrolled, and data are expected at the end of 2013. Safety and PK data in this age group are urgently

needed; the atazanavir/ritonavir ratio is 3:1 and as with darunavir this is complicated by the currently available formulations.

Lopinavir/Ritonavir

The generic manufacturer Cipla is developing a sprinkle formulation of lopinavir/ritonavir. The formulation (40/10 mg lopinavir/ritonavir) consists of a finite number of mini-tablets in a capsule, which is opened and sprinkled on soft food.

Data from a randomized crossover pharmacokinetic study in healthy adults comparing a single dose of sprinkles from 10 capsules of lopinavir/ritonavir with a single dose of 5 mL Kaletra oral solution (each mL containing 80 mg lopinavir and 20 mg ritonavir) were recently presented.[32] Both formulations were administered with about 150 g porridge and 240 mL water.

Most of the pharmacokinetic parameters fell within the conventional bioequivalence range of 80–125% in this study. Where they fell outside, the differences were not large.

Initial data from CHAPAS-2—which compared twice-daily sprinkles to tablets in children ages 4 to 13 years, and sprinkles with syrup in infants ages 3 to 12 months in a randomized cross-over PK study—found high variability in the younger cohort with both sprinkles and syrup, with no significant difference in subtherapeutic concentrations between formulations. In the older children, lopinavir/ritonavir concentrations were lower in children receiving the sprinkles than in those who got the tablets.[33]

Acceptability data showed storage, transport, and conspicuousness were less problematic for sprinkles compared with syrups, but for older children, several caregivers commented about the number of capsules needing to be used.

At week 8, when they could chose which formulation to continue with, 10 out of 14 (71%) caregivers chose to continue sprinkles rather than syrups for the infants, but only 7 of 29 (24%) of the older children chose sprinkles over tablet, and taste was particularly to blame.

The study comparing syrups to sprinkle in one- to four-year-olds is ongoing.

Integrase Inhibitors

Dolutegravir

The IMPAACT P1093 study will work with de-escalated age bands of children down to six-week-old infants. The older children will receive tablets, and the younger ones the pediatric formulation.

A granule formulation has been developed, and results from a phase I pharmacokinetic study in healthy adult volunteers were recently presented.[34] The granules were given with and without 30 mL of various liquids and compared to the current tablet formulation given with 240 mL of tap water. Subjects received a single dose of dolutegravir as a 50 mg tablet (adult formulation) and as 10 g of granule given: direct to mouth with no liquid; with purified water; with mineral water containing high-caution concentrations; or with infant-formula milk.

Dolutegravir exposures of the granule formulation were all moderately higher than those of the tablet formulation, with or without liquids. Exposure was highest when the granule formulation was given with formula milk.
The granule formulation is being studied further in children in IMPAACT P1093.

A reduced-strength FDC of dolutegravir (DTG), abacavir (ABC), and lamivudine is also planned.

Elvitegravir

The 183-0152 study was a phase Ib open-label nonrandomized trial in treatment-experienced adolescents receiving 150 mg once daily plus a PI-optimised background regimen. Of the 21 subjects enrolled in the 10-day pharmacokinetic study, 9 of 11 eligible subjects continued elvitegravir plus a ritonavir-boosted PI-containing optimized background regimen, and completed 48 weeks of treatment.

The pediatric committee of the EMA granted a positive opinion to the cobicistat and Quad pediatric investigational plan in April 2011.

Boosted elvitegravir will be studied in de-escalated weight bands, and a suspension formulation is in development for the youngest children.

The Quad study will start after a review of data for elvitegravir and cobicistat. Age-appropriate formulations are planned.

Raltegravir

The adult 400 mg film-coated tablet is approved in the United States for use in adults and in children ages 6 to 18 weighing >10 kg, and 100 mg and 25 mg chewable tablets are approved for children >2 to <12 years old at a maximum dose of 300 mg.

The pediatric program is ongoing in IMPAACT P1066, and an oral granule formulation is being studied in the youngest children and babies down to 4 weeks old. Intensive PK and preliminary 24-week safety and efficacy data on 6-month- to <2-year-olds receiving the raltegravir oral granule formulation were recently presented.[35]

In this dose-finding study of treatment-experienced children, they received weight-based raltegravir oral granule suspension at ~6 mg/kg, twice daily. The PK values achieved were similar to those observed in 2-year-old to <12-year-old children receiving chewable tablets; at week 12, 78% of the 9 children achieved virological suppression, and by 24 weeks, 85% achieved virological suppression.

The dose of 6 mg/kg every 12 hours was chosen for continued study in this age group.

Raltegravir also has the potential for use as prophylaxis to prevent vertical transmission to infants, and for treatment of HIV-infected infants. IMPAACT P1097 is an ongoing phase IV washout (passive) PK and safety study of infants born to women who received at least two weeks of raltegravir (400 mg twice daily) in pregnancy and through labor. This is the first clinical trial of an investigational antiretroviral to look at neonatal pharmacokinetics. Raltegravir crosses the placenta well. It is metabolized primarily by an enzyme in the liver (UGT-1A1) that is immature in neonates. UGT pathways increase in activity hugely in the first weeks of life.

Cord blood and single maternal blood samples were obtained within one hour of delivery alongside infant blood samples up to 36 hours after delivery. Early data from this study from nine mother-infant pairs showed maternal concentrations at delivery similar to those in cord blood (113%). The mean cord blood to maternal delivery concentration ratio was 1.14 (55%). The mean last infant raltegravir concentration at 30–36 hours was 407 ng/mL (range: 42.1–1,401 ng/mL). The mean neonatal half-life was 23.2 hours (range: 9.3–87.8 hours). No safety issues were identified at 20 weeks of life from in utero and transplacental exposure.[36]

Simulations combining these data plus PK data from four-week-old to six-month-old babies in P1066 will be used to determine the dose and frequency for neonates. The data from the washout study suggest that it may be possible to initially dose raltegravir once daily in newborns.

CCR5 Receptor Antagonist

Maraviroc

The A4001031 study is ongoing in children 2–18 years old who are infected with the CCR5-tropic virus (virus variants that use the CCR5 receptor for entry). Use of this drug requires an expensive tropism assay, as it will not work for people with the CXCR4-tropic virus or in dual- or mixed-virus (CCR5/CXCR4) populations.[37]

Preliminary data in 29 children showed body surface area–based doses of maraviroc provided adequate exposures when administered with a protease inhibitor as part of their background regimen. Children who were not receiving a boosting agent in their background regimen required at least doubling of the initial dose.[38]

A body surface area–scaled twice-daily tablet dose of maraviroc in treatment-experienced children 6 years and above concomitantly receiving boosted protease inhibitors (darunavir and lopinavir) achieved concentrations similar to those in adults receiving 150 mg maraviroc twice daily with a boosted protease inhibitor.[39]

TABLE 4. Pediatric ARV Pipeline

Agent/Class	Sponsor	Formulation(s)/ Dose	Status and Comments
atazanavir (ATV) Protease inhibitor (PI)	Bristol-Myers Squibb	Oral powder (50 mg sachet) Capsule 100, 150, 200, 300 mg	Ongoing phase II treatment-naive and -experienced with or without RTV from 3 months to 6 years of age
dolutegravir (DTG) Integrase inhibitor (INI)	Shionogi/ ViiV	Older children: tablets 10, 25, 50 mg Granule formulation being evaluated for younger children	Phase I and II from 6 weeks to 18 years of age Exposure of granules with different liquids exceeded that of tablets in healthy adults, so can be given without liquid restriction or directly by mouth
dolutegravir/ABC/3TC INI/2NRTIs FDC	Shionogi/ ViiV	Pediatric-specific formulation development planned (dosing to be determined)	Development dependent on ongoing studies confirming dose of DTG in children, and potential for once-daily dosing of ABC/3TC in children
elvitagravir (EVG) INI/booster	Gilead	Reduced-strength tablets and suspension in development	Phase I PK in healthy adults planned Needs boosting PK completed, RTV-boosted, 12–18 years of age RTV- and COBI- boosted EVG to be studied in all age groups
elvitagravir/cobicistat (COBI)/emtricitabine (FTC)/tenofovir (TDF) (Quad) INI/booster/2 NRTIs FDC	Gilead	Reduced strength tablets in development	Phase I PK (vs. adult Quad) in healthy adults planned Studies planned in treatment-experienced 6–18 years of age (waiver <6 years) once sufficient data available from individual compounds
etravirine (ETR) NNRTI	Janssen	Dispersible tablets 25 (scored), 100 mg	FDA approved for treatment-experienced children >6 years of age weighing >16 kg Phase I and II treatment-naive and -experienced 2 months to 6 years of age planned
lopinavir/ritonavir (LPV/r) Boosted PI	Cipla	Sprinkles 40/10 mg (equivalent to 0.5 mL liquid)	Similar PK to liquid in healthy adults PK in children being evaluated Sprinkle regimen for use in infants <2 years in resource-limited settings in development

maraviroc (MVC) CCR5 receptor antagonist	Pfizer/ViiV	Oral suspension 20 mg/mL	Phase IV Experienced CCR5-tropic, 2–8 years of age Requires tropism assay
raltegravir (RAL) INI	Merck	Oral granules for suspension 6 mg/kg (100 mg sachet) 100 mg and 25 mg chewable tablets	FDA approved 400 mg tablet for children 6 to 18 years old weighing >10 kg, and chewable tablets for >2 to <12 years old at a maximum dose of 300 mg. Awaiting EMA approval. Granules Phase II, 2 weeks to 2 years of age. Achieved good target exposure in 6 months to <2 years of age, similar to that with older children. Neonate passive PK study. Early data showed similar maternal delivery and cord blood concentrations. Infant half-life variable
rilpivirine (RIL) NNRTI	Janssen	Oral granules 2.5 mg base/g	Phase II planned, 0–12 years of age

Discussion

Despite the ever-diminishing pediatric antiretroviral market in industrialized countries, with little return on investment in research and development to produce what are often complex formulations, the pipeline looks quite promising.

But, as shown with tenofovir, which was finally approved for children down to two years of age, 11 years after its approval for adults; atazanavir, for which studies in the youngest age group have been painfully slow to recruit; and efavirenz, which is complicated to use in children less than three years old (for whom it appears that its optimal use requires pre-treatment genotyping and genotype-guided dose optimization), there are clearly technical, physiological, and operational barriers to developing appropriate formulations for young children in a reasonable time frame.[40,41]

On a more optimistic note, for some of the newer antiretrovirals, things do seem to be moving more swiftly than in the past. This might be a result of regulatory incentives and penalties: since 2007, EMA marketing authorization

cannot be granted for a new medicinal product without a Pediatric Investigation Plan (PIP).[42] This obligation comes with rewards, like six months' extension of patent protection. The PIP must be submitted when the adult phase I is completed and include details of methods proposed—with all pediatric subsets covered by a combination of studies and waivers— including age-relevant dosing and formulations. Although not so strict, the FDA has similar incentives.[43] Whether or not this has moved things along is a moot point, but regulations do seem likely more effective than reliance on what remains a vulnerable market or industry largesse.

Furthermore, formulations for young children for all but one drug in the current pipeline are granules, a dispersible tablet, or a powder, which might be useful for resource-limited settings in the future, although still not as desirable as dispersible scored tablets.

The work for children by the generic company Cipla is laudable and continues to be pioneering.

The work by DND*i* is very important, as it specifically targets the youngest age group of children living in these settings.

The ViiV/CHAI/Mylan plans are also promising, not least as a rehearsal for future strategies. In a separate chapter of this report, Simon Collins describes some of the advantages of dolutegravir—low milligram dose, no boosting required, low pharmacokinetic variability, etc.—which will also apply to children's formulations. A granule formulation is already in development, and an FDC is planned. Further along the pipeline, the follow-up integrase inhibitor S/GSK-1265744, under investigation as a long-acting formulation, has provoked interest as a potential treatment of adolescents (as has the long-acting formulation of rilpivirine). If these compounds do fulfill their early promise, the company should use its experience with the dual-nucleoside formulation, figure out the intellectual property issues, and transfer the technology and resources to a generic company for production, registration, and distribution at the lowest possible cost for low-income, least-developed countries. And other companies should take note.

What Needs to Be Done?

Reality check: although antiretroviral treatment coverage for adults continues to grow and now reaches about half those currently in need, for children—despite a dramatic increase in those receiving antiretrovirals since 2005—this proportion does not even reach a quarter. So the remaining majority of the 3.4 million children in need of treatment worldwide are still neglected.

Meanwhile pediatric HIV is becoming an old story set against a backdrop of targets to eliminate vertical transmission by 2015, which though they are to be applauded, must not happen at the cost of continual scale-up for children.

In order for this not to continue, a number of things urgently need to be addressed:

- **Definitive guidance.** The next WHO guideline revision is likely to recommend a lopinavir/ritonavir-based regimen first line irrespective of NNRTI exposure for all children under three. Older children might be able to align with adults and receive efavirenz/tenofovir/lamivudine. Guidance is also needed for second-line treatment.

- **Research gaps.** There is still uncertainty with regard to tenofovir use in children. The release of the WHO systematic review is important, as is analysis of existing cohort data. Whether NNRTI-exposed children can switch from lopinavir/ritonavir to an NNRTI following early treatment with a boosted protease inhibitor is unclear with a switch to nevirapine, but ongoing work in NEVEREST-III will shed light on whether or not this is possible with efavirenz.[44,45]

- **Suitable formulations.** Development, approval, and distribution of new formulations need to happen in ways that are timely and do not further fragment the market. The time from first FDA/EMA approval to when products are available where they are most needed must shorten. This will require earlier access by generic companies to new products (which must include the possibility to develop FDCs with components from different innovators) and registration by the WHO and in country. To reduce the current situation with too many formulations and too few real options, products need to be rationalized and unsuitable ones phased out.

- **Consolidated procurement.** CHAI needs to continue with its successful model of price negotiations.[46] Concerted efforts by international donors, including the Global Fund and PEPFAR, need to be made to facilitate the transition from previous reliance on UNITAID funding of pediatric products. In the many individual countries where orders do not meet manufacturer volume requirements, buyers must get together.

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RETROFITTING FOR PURPOSE: TREATMENT OPTIMIZATION

By Polly Clayden

In June 2010, WHO and UNAIDS launched Treatment 2.0, a strategic approach to the achievement of universal access to antiretroviral therapy (ART) and to making the most of the role of ART in preventing new infections.[1] A critical component of the strategy is the development of optimized, simpler, less toxic, and more efficient antiretroviral (ARV) drug regimens. It includes establishing optimal doses of ARVs (including possible dose reductions of existing ones), reducing pill count, using fixed-dose combinations (FDCs), and expanding access to safe, effective, and affordable drug regimens.

The ideal characteristics of a "dream regimen" have been variously described, and the target is one that is "so safe, effective, tolerable and durable that the need for switching to a new regimen would be very rare."[2,3,4]

TABLE 1. Target Product Profile of a Dream ARV Regimen

Safe and Effective	Better or Equivalent to Currently Recommended Drugs
Simple	Possible to be given in decentralized facilities or the community. One pill once a day (less frequently might be possible in the future). No lead in dosing. No dose adjustments when given with other common medicines. Heat-stable. Shelf life of two or more years
Tolerable	Minimal toxicity. Reformulation and/or dose reduction might improve tolerability
Durable	High genetic barrier to resistance. Low pharmacokinetic variability. Forgiving of missed doses. Tolerable for easier adherence
Universal	Safe and effective across all CD4 strata; in people with high viral load; in men and women; during pregnancy; across age groups and with common coinfections such as tuberculosis or viral hepatitis
Affordable	ARV coverage does not meet the estimated current need. Meanwhile, evidence is growing for earlier and wider use of treatment

A dream regimen, which encompasses all the characteristics of the target product profile, is a few years away but we might be able to do better with what we have already. We should also keep a close watch on what's on the horizon. This new chapter explores the ongoing research into treatment optimization including dose optimization with existing compounds, and possible future opportunities with new ones at the nearer end of the pipeline.

Discussions about dose optimization—particularly through appropriate dose reduction—of approved antiretrovirals have been ongoing now for over a decade,[5,6] the rationale being that when developing new drugs, the highest tolerated doses in phase II are often selected for phase III and, in turn, approval, where in some cases lower doses may have equivalent efficacy. Opportunities with some of the currently approved ARVs could offer several advantages over the approved doses:

- Reduction of the active pharmaceutical ingredients (API) used in a compound could lead to reduction in price (API accounts for approximately 70% of the price of generic ARVs);
- Potential reduction in toxicities; and
- Reduction in volume could make co-formulation easier (in resource-limited settings, 80% of people are treated with FDCs).

Research into these strategies has gained momentum recently, including endorsement by WHO/UNAIDS as part of Treatment 2.0. In addition, the Clinton Health Access Initiative (CHAI) has undertaken the execution and coordination of a number of projects, and the Bill & Melinda Gates Foundation is providing substantial donor support.[7,8] Several dose optimizations of antiretrovirals, including a number of clinical trials looking at dose reduction, are under way or in discussion.

Tenofovir

Tenofovir is preferred as part of first-line treatment (in combination with lamivudine and efavirenz). It is broadly considered to be the best NRTI (nucleoside reverse transcriptase inhibitor)/NtRTI (nucleotide reverse transcriptase inhibitor) on the market, and this is likely to continue for several years.

In recent years, its price has dropped considerably. A tenofovir-based FDC regimen is now available at an annual per-patient cost of less than US$159.[i] There are, however, limits to tenofovir's lowest possible price due to its high milligram dose (300 mg) with the current formulation. This also makes it less easy to co-formulate with other antiretrovirals.

i All prices quoted in this chapter are from the CHAI ARV Ceiling Price List: http://clintonhealthaccess.org/files/CHAI_ARV_Ceiling_Price_List_May_2012.pdf, and the Médecins Sans Frontières (MSF) Drug Prices & Patent Status list: http://utw.msfaccess.org/drugs.

Dose Optimization Strategies

There are several ways in which dose optimization might be accomplished:

- **Dose reduction.** In order to achieve regulatory approval for a dose lower than that currently approved, fully powered non-inferiority studies (phase III)—similar to those conducted by industry for the approval of a new drug—need to be done. It would take about three to six years to generate sufficient data to file with regulatory agencies, plus time to approval (about three months to a year). The estimated cost would be US$15–22 million.

- **Reformulation.** This strategy makes use of technologies and/or inactive ingredients to increase the bioavailability of a drug. A reformulated compound will need bioequivalence studies with the approved formulation (phase I). The estimated time frame to regulatory filing is two to three years, at a cost of US$2–8 million.

- **Process chemistry.** It may also be possible to alter the manufacturing process leading to more efficient and less expensive API production. For this strategy to be successful, regulatory authorities would need to see only equivalent stability and purity data. This would take about one to two years, at an estimated cost of US$1–2 million.

Source: Crawford KW, Brown Ripin DH, Levin AD, et al. Optimising the manufacturing, formulation, and dosage of antiretroviral drugs for more cost-efficient delivery in resource-limited settings: a consensus statement. Lancet Infect Dis. 2012;12(7):550–60.

CHAI is currently working on reformulation of tenofovir in partnership with a generic manufacturer. Although the new dose has yet to be determined, the researchers anticipate a reduction by about a third.

Additionally there are two new pro-drugs of tenofovir in development: GS-7340 (steaming ahead) and CMX-157 (almost moribund), which Simon Collins describes elsewhere in this report.

Zidovudine

If tenofovir remains the preferred first-line NRTI/NtRTI, zidovudine is likely to be used second-line in the short term.

Although zidovudine is generally better tolerated than stavudine over a long-term period, its hematologic toxicities (anemia/neutropenia) remain a concern in many resource-limited settings (RLS).

The ongoing MINIZID study is looking at 200 mg versus 300 mg zidovudine twice daily (as part of a regimen with lamivudine plus a non-nucleoside reverse transcriptase inhibitor [NNRTI]), with reduction of anemia as the primary

endpoint. This is a 48-week phase II study in 136 treatment-naive patients, sponsored by the University of Geneva and being conducted at the Hôpital de la Caisse Nationale de Prévoyance Sociale, Yaoundé, Cameroon. Recruitment began in August 2011.[9]

The study will not generate sufficient data for regulatory approval of the lower dose, but will provide proof of principle.

Some Asian countries such as Thailand and India already use the zidovudine 250 mg tablet twice daily, and Thailand is already using 200 mg twice daily in patients weighing less than 50 kg.

Stavudine

Of all the dose optimization strategies proposed or ongoing, the decision to use stavudine is the most controversial. Unlike the other antiretrovirals for which these strategies are being suggested or conducted, stavudine is no longer a preferred option due to its toxicity profile.

A proposed phase IIIb study plans to compare 20 mg stavudine twice daily to 300 mg tenofovir once daily in approximately 1,000 patients. The primary objective is to demonstrate the non-inferiority of stavudine to tenofovir (both in a regimen with lamivudine plus efavirenz) in treatment-naive patients. The proportion of patients in each regimen with undetectable viral load (<200 copies/mL) at 48 weeks would determine this.

The secondary endpoints are to evaluate the tolerability, overall safety, and efficacy of 20 mg stavudine compared to tenofovir.

The trial would be conducted at sites in India, South Africa, and Uganda and sponsored by the Bill & Melinda Gates Foundation.

This trial is concerning, as it will not answer stavudine's long-term toxicity question. The 20 mg stavudine dose might be acceptable in a short-term 48- or even 96-week virological endpoint study. However, because mitochondrial toxicity is both dose- and time dependent, many of stavudine's most serious side effects (such as peripheral neuropathy and lipoatrophy) would not necessarily emerge until after such a study was completed. Although it looks at lipoatrophy, this study does not include monitoring of surrogate markers for mitochondrial toxicity, so it cannot shed light on the incidence of this serious adverse event.

The stavudine parallel track program, which randomized over 10,000 patients to receive 40 (30) mg or 20 (15) mg (between October 1992 and February 1994), showed a higher incidence of neuropathy in the high-dose arm (21%). Nonetheless, the incidence of neuropathy observed in the lower dose arm was also unacceptably high (15%).[10]

In addition to concerns about cumulative toxicities, stavudine-related cost savings might become irrelevant by the trial's end. Through other dose optimization strategies and the expected approval of promising pipeline compounds (such as GS-7340 and douletegravir), alternatives are likely to become available in a similar time frame that could drive regimen costs down with less risk to patient safety.

Importantly, stavudine is extremely unpopular with people with HIV and activists.[11,12] For example the Malawi Network of People Living with HIV/AIDS (MANET+) held a press briefing concerned by the slow pace for phasing out current use of this drug in Malawi. Despite the funding crisis the Malawi government has prioritized this to be completed by June 2012.[13]

In South Africa and India, people with HIV and activists are preparing protests and petitions against the trial and the slow phase out of stavudine.[14,15]

As Bad Science's Ben Goldacre asked: "Why is the Gates Foundation supporting this trial of a rubbish AIDS drug?"[16]

Efavirenz

Efavirenz is currently the preferred anchor drug. Price and possibly central nervous system (CNS) toxicities could be reduced if a lower dose than the currently recommended 600 mg is possible.

The ENCORE1 study, which began recruitment in September 2011, is looking at 600 mg versus 400 mg of efavirenz in 630 treatment-naive patients. The ENCORE studies are designed to compare lower doses with approved doses of antiretrovirals. Pharmacokinetic studies of lamivudine and lopinavir (ENCORE2 and ENCORE3) have already been conducted as part of this program, with the conclusion that neither is a suitable candidate for dose reduction.[17,18,19]

The primary endpoint for ENCORE1 is the comparison between treatment groups of proportions of patients with viral load <200 copies/mL 48 weeks after randomization. The complete follow up is 96 weeks, and there are sites in Europe, Australasia, Latin America, Asia, and Africa. The trial is fully recruited, and results are expected in 2013.

ENCORE 1 has two substudies designed to look at pharmacokinetics (PK) and CNS exposure.[20,21]

If successful, this trial will generate sufficient data to gain regulatory approval and change World Health Organization (WHO) and other key treatment guidelines.

There are concerns about the drug/drug interaction with rifampicin in TB/HIV coinfection if the efavirenz dose is reduced.

The high API of efavirenz is due in part to its poor water solubility. CHAI is in discussion about reformulation work to improve this.

Atazanavir

Dose reduction may also be possible with atazanavir, and the HIV Netherlands Australia Thailand Research Collaboration, with some support from the Kirby Institute, is conducting a trial that will provide some evidence for this strategy.[22]

The low-dose atazanavir/ritonavir versus standard-dose atazanavir/ritonavir (LASA) study is comparing the efficacy and safety of atazanavir/ritonavir at either 200/100 mg or 300/100 mg once daily in Thai patients in combination with two NRTIs. This non-inferiority, phase IV study with about 600 patients began recruiting in March 2011 and has a time line similar to that of ENCORE1.

This study is enrolling patients who are already virologically suppressed to switch to the lower or standard dose of atazanavir. This research is important for Thailand as patients tend to have a lower body weight, and hyperbilirubinemia occurs quite frequently. It will be difficult to generalize the results from this research beyond the study population, but positive results would provide good reason to conduct a study in treatment-naive patients from a broader population.

Atazanavir is also poorly water-soluble, and CHAI is looking at the possibility of reformulation.

Darunavir

Darunavir is generally considered to be the most durable protease inhibitor (PI), but there is no generic formulation, and cost has been a barrier to its wide use.

This drug also has different approved doses for treatment-naive (including treatment-experienced but with no darunavir-associated mutations) and PI-experienced patients. Treatment-naive patients receive darunavir/ritonavir at an 8:1 (800/100 mg) ratio once daily, and experienced patients at a 6:1 ratio (600/100 mg) twice daily. There may be potential for dose reduction to 400/50 mg.

The ratios also vary for children depending on their weight band and treatment experience.

The establishment of single ratios for adults and children would make simpler darunavir-based regimens and formulations more feasible.

CHAI is also looking at optimizing the formulation.

Ritonavir

It may also be possible to give atazanavir and darunavir with a lower boosting dose of ritonavir. Lower doses could be better tolerated, cheaper, and easier to co-formulate with PIs than the current dose.

If a 50 mg heat-stable tablet of ritonavir could be manufactured or 50 mg coformulated with either protease inhibitor, new bioequivalence trials would be needed to ensure that boosting effects were similar to those that have been achieved previously in small pharmacokinetic trials with the liquid formulation. A 50 mg ritonavir tablet would also be very useful for pediatric dosing, as the liquid is expensive, impractical (particularly for resource-limited settings) and tastes dreadful.[23]

Lopinavir

The current tablet formulation of lopinavir/ritonavir is 118% bioavailable, compared to the original gel capsule formulation. Taking a regulatory approach using existing data could possibly be sufficient for the approval of a lower dose with this compound, and this strategy has been discussed. Although lopinavir is now the most widely used protease inhibitor, both atazanavir and darunavir are considered to be better options, so this approach may not be pursued as it is of low priority.

TABLE 2. Approved ARV Compounds with Potential for Dose Optimization

Agent/current dose/class	Potential approaches	Outcomes	Comments
atazanavir/ritonavir 300/100 mg once daily PI	Dose reduction Reformulation	Dose reduced to 200/100 mg or 200/50 mg once daily Potential US$70 savings per person per year	LASA phase III study of 300/100 mg versus 200/100 mg Potential for lower ritonavir boosting dose Already cheapest PI
efavirenz 600 mg once daily NNRTI	Dose reduction Reformulation	Dose reduced to 400 mg once daily Potential US$20 savings per person per year	ENCORE 1 phase III study currently ongoing May reduce CNS side effects (although not primary endpoint) May be possible to reduce dose further still (300 mg) Concerns about the impact on efficacy of TB/HIV cotreatment because of rifampin interactions
zidovudine 300 mg twice daily NRTI	Dose reduction	Dose reduced to 200 mg twice daily Potential US$25 savings per person per year	MINIZID phase III study recruiting Possible reduction of anemia incidence
tenofovir 300 mg once daily NtRTI	Reformulation	New dose to be determined by research >30% dose reduction anticipated	Phase I likely to start Q4 2012/Q1 2013 Possible reduction of incidence of renal and bone toxicities Also pro-drugs GS-7340 and CMX-157 in development
darunavir/ritonavir 800/100 mg once daily or 600/100 mg twice daily PI	Dose reduction Process chemistry	Dose reduced from 800/100 mg to 400/50 mg once daily	Dose optimization potential for PI-naive patients, but not for patients with PI resistance Potential for lower ritonavir boosting dose Dependent on regimen sequencing in patients who are PI-naive; dose reduction possible, but not if they have used a PI previously

lopinavir/ritonavir 400/100 mg twice daily PI	Regulatory approach	Daily lopinavir dose reduced from 800 mg to 665 mg (with current formulation)	Registrational trials were with earlier softgel capsule formulation. Newer tablet formulation has better bioavailability (118%) with approved dose. Possible to reduce the lopinavir dose by 20% Taking a regulatory approach is under discussion but less likely to be pursued
ritonavir 100 mg Booster	Dose reduction	Boosting dose of darunavir and atazanavir reduced to 50 mg Potential US$20 savings per person per year	Under discussion
stavudine 30 mg twice daily NRTI	Dose reduction and comparison with TDF	Dose reduced to 20 mg twice daily	Likely to maintain unacceptable side effects even at lower dose because of the cumulative effect Other drug developments likely to make this cost-saving strategy unnecessary within the timeline for study and approval Low acceptability by people with HIV, activists, and health workers

What to Expect in the Next WHO Guideline Revisions

It is expected that in the short term the preferred adult first-line treatment will remain an FDC of efavirenz/tenofovir/lamivudine, and that the next WHO guideline revisions will not be dramatic—and reports from recent expert meetings reflect this.[2,3,4,24,25]

Central nervous system toxicities that are a concern with efavirenz might be reduced with the lower dose under investigation in ENCORE1, and the trial includes a substudy to look at this aspect. Fears about its use during pregnancy are steadily being assuaged, and more permissive recommendations—in keeping with the most recent British HIV Association guidelines, and suggested in the recent WHO programmatic update on ARVs for pregnant women—are expected in the 2013 guidelines.[26,27,28,29,30]

Despite direct comparisons, lamivudine and emtricitabine are largely considered to be interchangeable in terms of efficacy and safety, and a recent WHO systematic review concluded this to be true.[31] Both are NRTIs and are structurally similar molecules with low toxicity, and both are effective against hepatitis B virus. Cost comparisons make lamivudine the preferred option—using emtricitabine instead in combination with efavirenz and tenofovir adds US$24 per patient per year to the cost of a first line regimen FDC, and US$27 to a combined product with tenofovir.

Work on the bioavailability of tenofovir could bring down the price (currently US$58 as a single agent), and further reductions still might be possible with the new pro-drug.

Boosted protease inhibitors plus two NRTIS are recommended for second-line treatment, and this is not expected to change in the short term. The FDA has recently tentatively approved a heat-stable formulation of atazanavir/ritonavir.[32] This 300/100 mg one-pill once-daily formulation is US$276 per patient per year and compares favourably to heat-stable lopinavir/ritonavir costing US$378, with four pills a day and twice-daily dosing. Once-daily heat-stable boosted darunavir might also be an option, but at present a suitable formulation (and suitable price) remains elusive. Dose reductions of atazanavir, darunavir, the ritonavir booster, and zidovudine (which will be used second-line if tenofovir is used first-line) are all being investigated or considered.

Recommendations for third-line treatment were introduced for the first time only in 2010, and suggest boosted darunavir, raltegravir (the only approved integrase inhibitor), and etravirine (second-generation NNRTI) in nucleoside sparing regimens. Again, little change is expected beyond the possible expansion of options in the integrase class (boosted elvitegravir and dolutegravir). None of these yet have generic versions, and the cost is considerable. More detailed guidance is needed in the next revision.

Opportunities with Pipeline Drugs—Ones to Watch

The integrase inhibitor dolutegravir, currently in phase III, with expected approval in 2013, is a compound with high potential, and it is predicted to cost US$30 per patient per year: 90% cheaper than raltegravir.[ii,33] It is a small molecule (50 mg), compared to elvitegravir (150 mg once daily plus 150 mg cobicistat) and raltegravir (400 mg twice daily), with once-daily dosing in

ii More extensive details and references for the investigational antiretrovirals are provided in the ARV chapter of this report, and for their respective investigational plans in children in the pediatric ARV chapter.

treatment-naive patients. Early data suggest that a dose increase (to 50 mg twice daily) will be needed with TB treatment.[34] Dolutegravir appears well tolerated, and with the potential to be low-cost could potentially replace efavirenz first-line or be used second-line. Trials in children, including in neonates, are planned and a granule formulation is in development.

Further down the pipeline, but also with high potential, is the tenofovir pro-drug GS-7340. An interaction with cobicistat makes it possible to use a 10 mg dose when it is co-formulated with this boosting agent.[35] The dose is still to be announced for the single agent, but is expected to be 25 mg.[36] With doses 10 times or more lower than that of the existing formulation of tenofovir, the cost of GS-7340 is predicted to be appropriately lower, and could come in at an annual patient cost of as little as US$20.[iii] A question with this compound is whether increased intracellular concentrations of GS-7340 accumulate in renal tubule cells and, in turn, cause associated toxicity. No renal problems were observed after 10-day exposure, but this is an important aspect of further studies. It is unfortunate that this compound was not prioritized for development earlier, as in vitro data were presented 10 years ago.[37]

With the potential to completely alter standard of care, discussions about, and early development of, long-acting formulations are also under way for monthly or weekly depot injections. Potential candidates might be rilpivirine and GSK1265744, both in early stages of development, plus CMX-157, which also has a long half-life, but the future of this molecule is currently unclear.[38,39,40] As yet, though, we do not have clarity on the target product profile, nor is it clear if the right combination of drugs required to construct a suitable regimen are available or even in development.[3]

Discussion

The ARV chapter of this report describes a number of FDCs, either filed with the FDA or in phase III, targeted at markets in industrialized countries. These are either "incestuous" combinations of compounds from the same manufacturer, e.g., Quad, Quad 2, and 572-Trii, or licensing agreements between companies where there is no competing alternative component, such as that between Gilead and Janssen to formulate darunavir/cobisistat/emtricitabine/GS-7340. And, as noted in that chapter, "virological failure with resistance to one FDC is likely to preclude reliance on others."

Gilead, Janssen, and BMS are also investigating cobicistat with darunavir and atazanavir as co-formulated boosted PIs, although it is unclear whether cobicistat offers any advantages over ritonavir.

iii i-Base/TAG estimate based on fixed cost of TDF API, inactive ingredients, and packaging.

With respect to RLS, Quad is not expected to become a preferred option, with dolutegravir on the horizon, elvitegravir requiring a boosting agent, and lamivudine preferred to emtricitabine. 572-Trii is also not entirely appropriate as the cost of abacavir and concerns about hypersensitivity have meant this NRTI is not recommended or widely used (except in pediatric treatment). The darunavir-based FDC is targeted at first-line patients (with 800/100 mg darunavir/ritonavir), and so is also unlikely to be a useful option according to current (and expected short-to-medium-term) guidance, sequencing discussions, and pricing.

Although intellectual property is not the primary focus of this report, Table 3 shows pipeline FDC products and their respective patent information, and illustrates the hurdles that would need to be overcome were these FDCs, or others, to be produced by generic companies for RLS. The Medicines Patent Pool, which negotiates with the innovator pharmaceutical companies to license their drugs through the pool so that generic companies can then access these licenses, and in turn produce cheaper versions, seems the most promising mechanism to make newer drugs affordable and produce FDCs when patents are held by different companies.[41]

What Needs to Be Done?

Treatment optimization must be in the interests of people with HIV. Seeking a comeback for a drug virtually abandoned in rich countries, for the sake of cost, and against much opposition from people with HIV and activists, is unacceptable. It is unclear why the Bill & Melinda Gates Foundation—which plans to fund the trial to look at stavudine 20 mg—consider this study to be a priority as it also does not fit with the one-pill, once-a-day target regimen. As we have written elsewhere, it seems an aberration in an otherwise carefully considered strategy for supporting research into the optimization of ART for RLS. This includes the ENCORE1 study of low-dose efavirenz, the reformulation of tenofovir to increase its bioavailability (working with CHAI), and the development of innovative, potentially long-acting formulations.

Drugs and regimens need to be designed with RLS in mind. The target product profile has been widely described by now. Currently approved and pipeline compounds fit for this purpose need to be produced in appropriate formulations.

Shorten time between full FDA/EMA approval and WHO prequalification, FDA tentative approval, and approval by local regulatory agencies. This is critical. As Nathan Geffen describes in his commentary, national agencies such as the Medicines Control Council (MCC) in South Africa often take many years to register new medicines.

TABLE 3. Pipeline Combined Products including FDCs, and Patent Information

Agents/ Classes	Sponsors	Comments
Quad (elvitegravir/ cobicistat/ tenofovir/ emtricitabine) Integrase inhibitor/ booster/2 NRTIs	Gilead Licensed to the Medicines Patent Pool (MPP); this means Indian manufacturers can produce and sell the combination to 112 developing countries	Filed with FDA in October 2011; approval anticipated 2012
572-Trii (dolutegravir/ abacavir/ lamivudine) Integrase inhibitor/ 2 NRTIs	Shionogi/ViiV has its own licensing agreements There might be agreement with a WHO pre-qualified facility to manufacture the product (in Zimbabwe, Kenya, Uganda, South Africa) ViiV does not include India in its royalty-free licensing policy. DTG patents are filed in India	PK completed but not presented Phase III with treatment-naive patients begun
Quad 2 (elvitegravir/ cobicistat/ emtricitabine/ GS-7340) Integrase inhibitor/ booster/2 NRTIs	As Quad, but will depend on whether GS-7340 is licensed in India or not	Phase III
darunavir/ cobicistat/ emtricitibine/ GS-7340 PI/booster/ 2 N(t)RTIs	Licensing agreement between Gilead (COBI/ FTC/GS-7340) and Tibotec (DRV) COBI and FTC are in the MPP. Dependent on whether GS-7340 is patented in India or not No patent on darunavir in India on single molecule	First PI-based FDC GS-7340 small molecule (10 mg dose in FDC) makes co-formulation possible

Source: Updated from the 2011 MSF antiretroviral sequencing meeting report: http://www.msfaccess.org/sites/default/files/MSF_assets/HIV_AIDS/Docs/AIDS_Event_SequencingMtg_Report_ENG_2011_FINAL.pdf.

Delays with the registration process, in addition to production by generic manufacturers and recommendations in national guidelines, means that it takes years from promising results in trials and initial approval to wide availability for the majority of people in need of antiretroviral treatment. Despite almost 150 single agents and combination products having FDA tentative approval, the majority are older drugs and those with expired patents.

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PREVENTIVE TECHNOLOGIES, RESEARCH TOWARD A CURE, AND IMMUNE-BASED AND GENE THERAPIES

By Richard Jefferys

In previous years, this section of the pipeline report has lamented the absence of any approved products in the areas that it covers. In 2012, that may finally be about to change: on May 10, the U.S. Food and Drug Administration (FDA) held a marathon 12.5 hour Antiviral Drugs Advisory Committee meeting to discuss the efficacy of the antiretroviral Truvada (a combination pill containing tenofovir and emtricitabine) for preexposure prophylaxis (PrEP) against HIV infection, and the majority of members voted for approval. The vote tallies were 19 to 3 in favor for men who have sex with men, 19 to 2 (with 1 abstention) for HIV-negative partners in serodiscordant couples, and 12 to 8 (with 2 abstentions) for other individuals at risk for acquiring HIV through sexual exposure. A final FDA decision is expected by September 14, 2012.

If Truvada is approved for PrEP, as expected, much work will still be required to define how best to implement the approach. An array of demonstration projects are now getting under way with the aim of assessing real-world use of the intervention among different populations at high risk for HIV acquisition. Research is also continuing to look at whether there are alternatives to continuous dosing of PrEP and whether antiretrovirals other than Truvada might have PrEP potential. Despite many outstanding questions, the approval of Truvada would represent a historic moment for the biomedical prevention field. The idea of combination prevention has been under discussion for many years, but with circumcision being the only biomedical approach with proven efficacy, options were limited. Approval of PrEP, taken together with emerging signs of efficacy with vaccines and microbicides, would alter the landscape dramatically. Combinations are already being tested in animal models,[1] and it was recently announced that from 2014 onward a single biennial HIV prevention conference will integrate the topics of vaccines, microbicides, and PrEP. Hopes of developing highly effective candidates have not been abandoned, but rather in the interim there is intense interest in assessing whether partially effective approaches can synergize in ways that increase their ability to reduce HIV infection risk.

At the time the *2011 Pipeline Report* was published, there was optimism that a microbicide gel form of tenofovir might be en route to licensure based on

significant efficacy observed in the CAPRISA 004 trial in South Africa.[2] But news of a setback emerged on November 25, 2011, when it was announced that the tenofovir gel arm of an ongoing trial named VOICE was being discontinued due to a lack of any effect on HIV incidence.[3] The reasons for the divergent results are not yet clear, but may relate to different dosing strategies; participants in VOICE were instructed to use the gel daily, whereas in CAPRISA 004 application was within 24 hours before and after sex. Full analysis of the VOICE results will not be possible until the trial ends in August 2012. A phase III efficacy trial of tenofovir gel using the same dosing regimen as CAPRISA 004 is now taking place at nine sites in South Africa, but it is not yet known if a positive result will be sufficient to obtain approval. Although the fate of tenofovir gel is uncertain, the microbicide field has been buoyed by the recent launch of an efficacy trial of a vaginal ring that delivers the antiretroviral dapivirine; the ring needs replacing only once every four weeks, suggesting it will be considerably easier to use than prior methods. The study is sponsored by the International Partnership for Microbicides (IPM), and represents the culmination of their many years of work to develop the approach. A second complementary efficacy trial under the aegis of the Microbicide Trials Network (MTN) is due to begin within the next few months.

The HIV vaccine field continues to advance on multiple fronts. A key priority is following up on the marginal but significant efficacy observed in the RV144 trial in Thailand, which showed a 31% reduction in HIV acquisition associated with receipt of a prime-boost regimen comprising a canarypox vector, ALVAC-HIV vCP1521, and an envelope protein boost (AIDSVAX).[4] Over the past year, results of an analysis of possible correlates of protection have been presented and published, identifying immune responses among participants that may have been associated with vaccine efficacy.[5] Work is ongoing to better understand these findings in the hope of informing the design of new vaccines. Plans for efficacy trials of prime-boost combinations similar to those used in RV144 are well under way, with the goal of confirming and extending the results. However, these trials are not expected to open until 2014 due to delays associated with securing an envelope protein-boost component (AIDSVAX has been discontinued, and the company that manufactured it no longer exists; Novartis has been selected to produce a similar alternative).

Beyond RV144, researchers are pursuing preclinical development of novel vectors, such as those based on the virus CMV, that may be able to recapitulate the robust protection seen in animal models with live attenuated vaccine approaches (which cannot be directly translated to human use due to safety concerns). Efforts to solve the daunting challenge of inducing broadly neutralizing antibodies against HIV are progressing, but while the

understanding of how to achieve broad neutralization has greatly improved, methods for creating this activity with vaccines remain elusive.

Over the past few years, investigations into curing HIV infection—once viewed as the quixotic pursuit of a few—have become a major component of therapeutic research. The shift was much in evidence at the 2012 Conference on Retroviruses and Opportunistic Infections (CROI), which for the first time featured several crowded sessions on the topic. Some signs of promise have emerged from trials of drugs that may be capable of awakening the latent HIV reservoir that has so far stymied cure efforts,[6] but perhaps the most important finding presented at CROI (and published shortly afterward in the journal Immunity) is that even if dormant HIV is successfully roused, effective immune responses against the virus are needed to deliver the coup de grace and eliminate latently infected cells.[7] Because most individuals with chronic HIV infection lack the functional T-cell responses required to accomplish this task, this study has bolstered the rationale for the use of therapeutic vaccines in cure research.

As this report was going to press, the continuing uncertainty regarding exactly how a cure is defined was thrown into sharp relief by a disheartening and unnecessary public controversy over traces of HIV genetic material that may—or may not—have been found in the lone individual widely considered to have been cured of HIV infection, Timothy Ray Brown.[8] Brown has remained off all antiretroviral therapy (ART) for five years and counting, with no signs of active HIV infection—and these are widely considered the most important criteria for a cure. Researchers are attempting to duplicate the results of Brown's case by providing stem-cell transplants from donors homozygous for the CCR5-Delta32 mutation to additional individuals with HIV.

Immune-based and gene therapies are also being studied as possible adjuncts to ART. The goal is to address the dysregulation of the immune system that can persist in some individuals even after HIV replication is suppressed. The risk of persistent immune dysregulation increases with later initiation of ART, and features include elevated levels of immune activation and inflammation, poor CD4 T-cell increases, and an accelerated aging of the immune system referred to as immunosenescence.[9] An increasing number of studies have shown links between these phenomena and an elevated risk of morbidity and mortality,[10,11,12] suggesting that additional immune-based therapeutic interventions could improve the outcomes achieved with ART alone, at least in a subpopulation of people with HIV.

TABLE 1. HIV Vaccines Pipeline 2012

Agent	Class/Type	Manufacturer/ Sponsor(s)	Status
ALVAC-HIV vCP1521	Canarypox vector including HIV-1 CRF01_AE Env, clade B Gag, the protease-encoding portion of the Pol gene, and a synthetic polypeptide encompassing several known CD8 T-cell epitopes from the Nef and Pol proteins	Sanofi Pasteur/U.S. Military HIV Research Program (USMHRP)/National Institute of Allergy and Infectious Diseases (NIAID)	Phase IIb
pGA2/JS7 DNA/ MVA/HIV62	Prime: DNA vaccine Boost: MVA vector Both including Gag, Pol, and Env genes from HIV-1 clade B	GeoVax/NIAID	Phase IIa
LIPO-5	Five lipopeptides containing CTL epitopes (from Gag, Pol, and Nef proteins)	Agence Nationale de Recherches sur le Sida et les hépatites virales (ANRS)	Phase II
VRC-HIVDNA016-00-VP + VRC-HIVADV014-00-VP	Prime: Six separate DNA plasmids including Gag, Pol, and Nef genes from HIV-1 clade B, and Env genes from clades A, B, and C Boost: Adenovirus serotype 5 vectors including Gag/Pol genes from HIV-1 clade B and Env genes from clades A, B, and C	GenVec/Vical/NIH Vaccine Research Center (VRC)/NIAID	Phase II (HVTN 505)
VICHREPOL	Chimeric recombinant protein comprised of C-terminal p17, full p24, and immunoreactive fragment of gp41 with polyoxidonium adjuvant	Moscow Institute of Immunology/ Ministry of Education and Science of the Russian Federation	Phase II
DNA-C + NYVAC-C	Prime: DNA vaccine including clade C Env, Gag, Pol, and Nef genes Boost: NYVAC-C attenuated vaccinia vector including clade C Env, Gag, Pol, and Nef genes	GENEART/ Sanofi Pasteur/ Collaboration for AIDS Vaccine Discovery (CAVD)	Phase I/II

HIVIS 03 DNA + MVA-CMDR prime-boost HIV-1 vaccine candidate	Prime: HIVIS 03 DNA including Env (A, B, C), Gag (A, B), reverse transcriptase (B), and Rev (B) genes Boost: MVA-CMDR including Env (E), Gag (A), and Pol (E) genes	Vecura/Karolinska Institute/Swedish Institute for Infectious Disease Control/USMHRP	Phase I/II
MYM-V101	Virosome-based vaccine designed to induce mucosal IgA antibody responses to HIV-1 Env	Mymetics Corporation	Phase I/II
Ad35-ENVA	Prototype adenovirus serotype 35 vector including the HIV-1 subtype A Env gene	Crucell/ International AIDS Vaccine Initiative (IAVI)/NIAID/Beth Israel Deaconess Medical Center/ Ragon Institute of MGH, MIT and Harvard	Prime-boost phase I with Ad26. ENVA.01
Ad35-GRIN/ENV	Two adenovirus serotype 35 vectors, one including HIV-1 subtype A Gag, reverse transcriptase, integrase, and Nef genes, and the other including HIV-1 subtype A Env (gp140)	IAVI/University of Rochester	Phase I Prime-boost phase I with GSK HIV vaccine 732461
Ad26.ENVA.01	Prototype adenovirus serotype 26 vector including the HIV-1 subtype A Env gene	Crucell/IAVI/ NIAID/Beth Israel Deaconess Medical Center/Ragon Institute of MGH, MIT and Harvard	Phase I Prime-boost phase I with Ad35-ENVA
Ad5HVR48. ENVA.01	Prototype hybrid adenovirus vector consisting of a backbone of serotype 5 with the hexon protein from serotype 48; includes HIV-1 subtype A Env gene	Crucell/NIAID	Phase I
ADVAX e/g ADVAX p/n-t	Two DNA constructs: ADVAX e/g includes HIV-1 subtype C Env and Gag genes; ADVAX p/n-t includes HIV-1 subtype C Pol and Nef-Tat; administered by Ichor TriGrid electroporation	Ichor Medical Systems/Aaron Diamond AIDS Research Center/ IAVI	Phase I

Cervico-vaginal CN54gp140-hsp70 conjugate vaccine (TL01)	HIV-1 clade C gp140 protein with heat shock protein 70 (hsp70) adjvant, delivered intravaginally	St George's, University of London/European Union	Phase I
DNA + Tiantian vaccinia vector	DNA and recombinant Tiantian vaccinia strain vectors encoding Gag, Pol, and Env genes from HIV-1 CN54	Chinese Center for Disease Control and Prevention/ National Vaccine and Serum Institute/ Peking Union Medical College	Phase I
DCVax plus poly-ICLC	Recombinant protein vaccine including a fusion protein comprising a human monoclonal antibody specific for the dendritic cell receptor DEC-205, and the HIV Gag p24 protein, plus poly-ICLC (Hiltonol) adjuvant	Rockefeller University	Phase I
EN41-FPA2 HIV vaccine	Gp41-based vaccine delivered intranasally and intramuscularly	PX'Therapeutics/ European Commission	Phase I
GEO-D03 DNA, MVA/HIV62B	Prime: DNA vaccine with GM-CSF adjuvant Boost: MVA vector Both vaccines include Gag, Pol, and Env genes from HIV-1 clade B and produce virus-like particles (VLPs)	GeoVax/NIAID	Phase I
GSK HIV vaccine 732461	Gag, Pol, and Nef proteins in proprietary adjuvant	GlaxoSmithKline	Phase I Prime-boost phase I with Ad35-GRIN
HIV-1 Tat/delta-V2 Env	Tat and oligomeric ΔV2 Env proteins	Istituto Superiore di Sanità, Novartis Vaccines	Phase I

MAG-pDNA vaccine, Ad35-GRIN/ENV	Multiantigen DNA vaccine comprising the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVA, interleukin-12 (IL-12) pDNA adjuvant, delivered using the electroporation-based TriGrid delivery system, two adenovirus serotype 35 vectors, one including HIV-1 subtype A Gag, reverse transcriptase, integrase, and Nef genes, and the other including HIV-1 subtype A Env (gp140)	IAVI/Profectus Biosciences/ Ichor Medical Systems	Phase I
MAG-pDNA vaccine, $rVSV_{IN}$ HIV-1 Gag	Multiantigen DNA vaccine comprising the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, interleukin-12 (IL-12) pDNA adjuvant, attenuated replication-competent recombinant vesicular stomatitis virus (rVSV) vector including HIV-1 Gag protein	Profectus Biosciences/HVTN	Phase I
MV1-F4-CT1	Recombinant measles vaccine vector including HIV I Clade B Gag, Pol, and Nef	Institut Pasteur	Phase I
MVA.HIVA	MVA vector including a synthetic copy of a major part of HIV's Gag gene and 25 CD8 T-cell epitopes	Impfstoffwerk Dessau-Tornau (IDT) GmbH/University of Oxford/Medical Research Council/ University of Nairobi/Kenya AIDS Vaccine Initiative	Phase I in infants born to HIV-infected (PedVacc002) and HIV-uninfected mothers (PedVacc001)
MVA HIV-B	MVA vector including HIV-1 Bx08 gp120 and HIV-1 IIIB Gag, Pol, and Nef	Hospital Clinic of Barcelona	Phase I

PENNVAX-G DNA vaccine, MVA-CMDR	Prime: DNA vaccine including HIV-1 clade A, C, and D Env proteins and consensus Gag protein Boost : MVA-CMDR live attenuated MVA vector including HIV-1 clade CRF_AE-01 Env and Gag/Pol proteins DNA component administered intramuscularly via either Biojector 2000 or CELLECTRA electroporation device	NIAID/MHRP/ Walter Reed Army Institute of Research (WRAIR)	Phase I
PolyEnv1 EnvDNA	Vaccinia viruses including 23 different Env genes and DNA vaccine with multiple Env genes	St. Jude Children's Research Hospital	Phase I
pSG2.HIVconsv DNA, ChAdV63.HIVconsv, MVA.HIVconsv	Prime : DNA vaccine pSG2 Boost : chimpanzee adenovirus vector ChAdV63 or MVA vector All contain the HIVconsv immunogen, designed to induce cross-clade T-cell responses by focusing on conserved parts of HIV-1	University of Oxford	Phase I
rAd35 VRC-HIVADV027-00-VP	Adenovirus serotype 35 vector	VRC/NIAID	Phase I
$rVSV_{IN}$ HIV-1 Gag	Attenuated replication-competent recombinant vesicular stomatitis virus (rVSV) vector including HIV-1 Gag protein	Profectus Biosciences/HVTN	Phase I
SAAVI DNA-C2, SAAVI MVA-C, subtype C gp140/ MF59	SAAVI DNA and MVA vectors encoding an HIV-1 subtype C polyprotein including Gag-Reverse Transcriptase-Tat-Nef and an HIV-1 subtype C truncated Env. Novartis protein subunit vaccine comprising a subtype C oligomeric V2 loop-deleted gp140 given with MF59 adjuvant	South Africa AIDS Vaccine Initiative (SAAVI)/ HVTN/ Novartis	Phase I

Correlates of HIV Infection Risk in RV144

On September 13, 2011, at the AIDS vaccine conference in Bangkok, Bart Haynes from Duke University presented the results of a massive research effort to uncover correlates of HIV infection risk in the RV144 study; the data were subsequently published in the *New England Journal of Medicine*.[13] Although the efficacy of the vaccines was meager over the full course of the trial, it appeared to be higher in the first year, during which there were 12 HIV infections among vaccine recipients compared to 30 in the group receiving placebo (equating to an approximately 60% reduction in risk). By identifying correlates of this apparent protection, researchers hope to find clues that will help them reproduce and maintain the levels of efficacy observed early in RV144.

Haynes led a large collaborative research effort that prioritized six different immunologic tests and then studied them in a case-control format, comparing samples from 41 vaccine recipients who became infected to 205 who did not. Samples were taken at week 26, two weeks after the final booster immunization. Multiple comparisons are involved in the analyses, and this is known to increase the possibility of obtaining statistically significant results simply by chance. The standard statistical tool for addressing this possibility is called a Bonferroni correction, but it was not used in this case because the goal was to generate hypotheses about possible immune correlates for additional studies, as opposed to confirming associations definitively. Instead of the Bonferroni method, the scientists used an approach in which each result is assigned a "q-value," which represents the estimated chance of a false positive.

Two of the six measures showed significant associations with HIV acquisition: binding of IgA antibodies in plasma to HIV Env, which was linked to an increased relative risk of HIV infection of 1.54 ($P = 0.027$); in other words, vaccine recipients displaying this response at week 26 of the trial were 54% more likely to subsequently become infected than those without it. Conversely, the presence of binding IgG antibodies to the V1/V2 loops of HIV Env scaffolded onto the MLV gp70 protein was associated with a relative risk of 0.57 ($P = 0.015$), indicating that vaccine recipients who showed this response at week 26 were 43% less likely to acquire HIV than those who did not. For both results, the q value was 0.08, meaning that there is an approximately 8% chance they were false positives. The analyses were repeated and confirmed by a second, independent group of statisticians. Importantly, the presence of IgA antibodies to Env did not enhance HIV infection risk compared to placebo recipients; rather, vaccinated individuals with high levels of these responses

experienced the same risk of infection as the unvaccinated group. The opposite pattern was true for binding IgG antibodies to the V1/V2 loops: compared to placebo recipients, vaccinated individuals with the highest levels of these antibodies were around 50% less likely to acquire HIV infection.

The reason that IgA antibodies to Env would be associated with reduced vaccine efficacy is not yet clear, but it has been suggested that these antibodies interfere with antibody-dependent cellular cytotoxicity (ADCC), one of the immunologic mechanisms that could have been responsible for the protection observed in the trial. Similarly, it is not yet known whether the binding IgG antibodies to the V1/V2 loops were directly responsible for protecting against HIV infection (whether via ADCC or some other mechanism). However, these responses did wane significantly in vaccine recipients over the six months after the final week-24 immunizations, which appears to track with the protective effect of vaccination's being almost entirely concentrated in the first year of the trial.[14]

In separately published reports, RV144 researchers also identified the V2 region of HIV as a preferential target for vaccine-induced CD4 T-cell responses[15] and noted that certain class II HLA alleles were associated with a failure to mount antibody responses after vaccination.[16]

While much work remains, the new results represent potentially crucial clues for researchers working to improve on the marginal effect observed in RV144. Most optimistically, they hint that it might be possible to push the efficacy threshold of similar vaccine regimens over 50% by fine-tuning the types of immune responses that are induced. Although the induction of broadly neutralizing antibodies against HIV is still thought to be necessary to achieve a highly efficacious vaccine, the development of a candidate offering greater than 50% protection would be a huge step forward.

Replicating and Extending the RV144 Results

A variety of trials are under way or planned that should shed additional light on whether the RV144 results can be duplicated and improved upon. The U.S. HIV Military Research Program (USMHRP), one of the primary sponsors of RV144, is conducting follow-up trials involving ALVAC-HIV vCP1521 and the limited supplies of AIDSVAX that are still available. The RV305 trial is administering a "late boost" with ALVAC-HIV vCP1521, AIDSVAX, or both to volunteers from RV144 who received the full regimen in the original trial. Two additional smaller studies are slated to start soon; the primary goal is to investigate the immune responses induced by the vaccines—particularly mucosal responses—

in greater detail than was possible with the samples available from RV144. Longer term, the USMHRP has mapped out two potential phase IIb licensure trials for the prime-boost combination of ALVAC and a gp120 protein boost, one in high-risk men who have sex with men (MSM) in Thailand, and the other among high-risk heterosexuals in South Africa.[17]

During the past year, the HIV Vaccine Trials Network (HVTN) has begun phase I evaluations of DNA and poxvirus vectors developed by the South African AIDS Vaccine Initiative (SAAVI), combined with an HIV subtype C gp140 envelope protein booster manufactured by Novartis, a first step toward the type of regimens that will be used in phase IIb efficacy trials in South Africa which, if all goes well, will be launched in 2014. Sanofi Pasteur is manufacturing a subtype C–based ALVAC vector for these trials while Novartis is in the closing stages of developing the bivalent subtype C gp120 protein boost. The HVTN has outlined the novel adaptive design that will be employed;[18] the goal is to rapidly eliminate candidates and combinations that fail to show evidence of efficacy, and prioritize those that do.

There is one ongoing HIV vaccine efficacy trial, HVTN 505, which involves a prime-boost regimen comprising a DNA vaccine followed by an adenovirus serotype 5 (Ad5) vector. The study population is circumcised MSM and male-to-female (MTF) transgender persons who lack detectable antibody responses to Ad5 (the natural form of the virus is common in nature, so some individuals have preexisting antibody responses against it). Until recently, the primary goal was to look at whether the vaccines reduced viral load in recipients who subsequently acquired HIV, but in August 2011, it was announced that in light of the RV144 results, HVTN 505 is being expanded in size from 1,500 to 2,200 participants so that the effect of vaccination on risk of HIV acquisition can also be evaluated.[19] As of May 30, 2012, the enrollment total was reported to be 1,845.[20]

The Adenoviral Odyssey

In September 2007, the HIV vaccine field received an unexpected setback when it was announced that the phase IIb efficacy trial of a candidate developed by Merck was being stopped early due to lack of efficacy. The trial was conducted by the HVTN and was referred to as the STEP study. The Merck vaccine aimed to stimulate T-cell immunity against HIV, and used a novel attenuated Ad5 vector to deliver the HIV proteins Gag, Pol, and Nef. The adenovirus-based approach was selected because it induced unprecedented levels of CD8 T-cell responses in phase I and II trials, with >70–80% of recipients responding (the previous best was 20–30% of recipients showing

low-level CD8 T-cell responses after immunization with an ALVAC vector). Although HIV-specific CD8 T-cell responses were not anticipated to protect against acquisition of HIV infection, evidence indicated that they might be able to suppress HIV replication and thereby increase the chances of vaccine recipients becoming elite controllers if they became HIV-infected.

The STEP study was stopped after an interim analysis by the Data and Safety Monitoring Board (DSMB) revealed that this hoped-for salutary outcome was not being observed. Furthermore, it transpired that certain subgroups of the trial population experienced a significantly increased risk of HIV acquisition associated with receipt of the vaccine. In the overall results, this finding represented a strong trend that did not quite reach statistical significance. However, in a prespecified analysis that evaluated results based on baseline levels of antibodies to Ad5, there was a stepwise increase in the risk associated with vaccination as anti-Ad5 antibody titers increased, strongly suggesting a real biological effect. Subsequent post hoc studies revealed that the effect appeared entirely concentrated among uncircumcised MSM. To their great credit, the HVTN engaged in a massive and extremely transparent effort to investigate this outcome, involving both investigators affiliated with the network and the solicitation of input from external scientists with relevant expertise.[21]

In the time since, a variety of investigations have been conducted, but so far no causative mechanism has been identified to explain the STEP results. Unfortunately, along the way, some figures in leadership roles in the HIV vaccine field mistakenly attempted to suggest that the adenovirus vector had been absolved of having any role in enhancing HIV acquisition risk. For example, in 2009, Alan Bernstein (then head of the Global HIV Vaccine Enterprise) had this to say to the Scientist:[22]

"[This] result really rules out the possibility that it was the vaccine itself, and the fact that we used Adeno5, that was somehow increasing susceptibility to acquiring [HIV] in those volunteers."

In 2012, two papers on the STEP trial have been published that highlight the erroneousness of Bernstein's claim and the continuing uncertainty regarding the safety of adenovirus-based vectors. In an analysis published in the *Journal of AIDS*, researchers from the HVTN and Merck reported that no potential confounder could account for the increased risk of HIV acquisition associated with receipt of the Ad5 vector among uncircumcised men who have sex with men.[23] A separate report in the *Journal of Infectious Diseases* revealed that when assessed across the full course of the trial, the enhancement effect associated with the vaccine was statistically significant, but waned with

increasing time since the last immunization.[24] Importantly, the results confirmed that no enhanced risk of HIV infection was seen at any time among circumcised individuals who lacked antibodies to Ad5 at baseline (the population being recruited for the HVTN 505 trial).

The most commonly cited hypothesis to explain the STEP outcome was that the vaccine boosted numbers of Ad5-specific CD4 T cells, thereby increasing the pool of cells potentially susceptible to HIV. But several papers have reported data that are inconsistent with this idea: blood levels of Ad5-specific CD4 T cells did not associate with acquisition risk,[25] and these responses were also rapidly induced in study participants who lacked anti-Ad5 antibodies at baseline (yet these participants experienced no increase in risk).[26] Another notion was that perhaps anti-Ad5 antibody levels correlate with HIV risk for unknown reasons, but an analysis of the Multicenter AIDS Cohort Study (MACS) did not find an association,[27] and this finding was echoed when researchers investigated the question using samples from several HIV vaccine trials.[28]

Studies have also proposed the possibility that the increased susceptibility is related to trafficking of Ad5-specific CD4 T cells to mucosal sites where adenovirus antigens are expressed,[29] but this has yet to be thoroughly explored in humans. Two macaque experiments have produced data that argue against the theory,[30,31] but some uncertainty remains because these animals are not naturally infected with Ad5.

Continued efforts to understand the mechanism of enhancement in the STEP trial are important, because while Merck's Ad5-based HIV vaccine has been discontinued, adenovirus vectors from an array of different serotypes—including several from chimpanzees—continue to be studied as potential vaccines against HIV, TB, malaria, and hepatitis C, and it is currently unclear if they might also have the potential to increase HIV acquisition risk.

Another recent wrinkle in the adenovirus vector story is a published study indicating that preexisting adenovirus-specific CD4 T-cell responses—which, like antibodies, are also common due to natural exposure—can impair the generation of immune responses to antigens contained in adenovirus-based vaccines.[32] Unlike antibodies, CD4 T cells cross-react with multiple human and chimpanzee adenovirus serotypes, raising the fear that these responses could impact the effectiveness of many candidates. Among the variants currently in trials are Ad35 and Ad26, which have produced promising results in the SIV/macaque model,[33] and two chimpanzee serotypes: ChAd63 and ChAd3.[34] Encouragingly, a phase I evaluation of ChAd63 as a potential malaria vaccine

found that preexisting immunity to adenovirus did not appear to hamper the development of strong immune responses to the vector-encoded malaria antigens.[35]

Passive Immunization with Broadly Neutralizing Antibodies

An increasing number of antibodies capable of broadly neutralizing many different HIV variants are being identified. Among the most notable is VRC01, which potently inhibits around 90% of a panel of diverse viral isolates.[36] The future plans of the HVTN include studies that will deliver the broadly neutralizing antibodies to individuals at risk for HIV acquisition by infusion, an approach called passive immunization. Under a program launched in 2006 by the Bill & Melinda Gates Foundation called the Collaboration for AIDS Vaccine Discovery (CAVD), Gary Nabel from the Vaccine Research Center at the National Institutes of Health (NIH) was recently awarded a grant of US$1.9 million over three years specifically to develop a formulation of VRC01 to use in passive immunization studies. The primary goal is to assess whether protection can be achieved and gain an understanding of the antibody levels that might be required. One setting that is under consideration for these trials is prevention of mother-to-child transmission (PMTCT), but there are some researchers who feel strongly that this type of experiment cannot be ethically justified because, when properly implemented, antiretroviral therapy is highly effective at preventing PMTCT.[37] Others argue that there is some residual risk of transmission that could potentially be addressed by passive immunization.[38] Before these trials proceed, it will be important for there to be a broad public discussion of the issues involved. Although it would be advantageous to learn more about the protective efficacy of broadly neutralizing antibodies, methods for inducing similar antibodies with vaccines have yet to be discovered. Unless passive immunization could be made widely available—which seems an unlikely prospect given both the inconvenience of the delivery method and the cost—the potential for the populations targeted for these proposed trials to gain benefit from their participation will need to be carefully considered.

TABLE 2. PrEP and Microbicides Pipeline 2012

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
dapivirine (TMC120) (vaginal ring)	Reverse transcriptase inhibitor	International Partnership for Microbicides (IPM)	Phase III
tenofovir gel	Nucleotide reverse transcriptase inhibitor	CONRAD/South Africa Department of Science and Technology, South Africa National Department of Health/ USAID/Bill & Melinda Gates Foundation	Phase III
tenofovir/ emtricitabine (Truvada)	Combined nucleoside and nucleotide reverse transcriptase inhibitors	ANRS	Phase III
tenofovir (Viread)	Nucleotide reverse transcriptase inhibitor	Gilead Sciences/NIAID/ CDC	Phase III
tenofovir/ emtricitabine (Truvada)	Combined nucleoside and nucleotide reverse transcriptase inhibitors	HIV Prevention Trials Network	Phase II
maraviroc	CCR5 inhibitor	HIV Prevention Trials Network	Phase II
dapivirine (TMC120) gel	Reverse transcriptase inhibitor	IPM	Phase I/II
ibalizumab (formerly TNX-355)	Monoclonal antibody	TaiMed Biologics Inc./Aaron Diamond AIDS Research Center/Bill & Melinda Gates Foundation	Phase I
maraviroc (vaginal ring)	CCR5 inhibitor	IPM/MTN/NIAID/National Institute of Mental Health (NIMH)	Phase I
maraviroc + dapivirine (vaginal ring)	CCR5 inhibitor + reverse transcriptase inhibitor	IPM/MTN/NIAID/NIMH	Phase I
tenofovir gel (rectal formulation)	Nucleotide reverse transcriptase inhibitor	Microbicide Trials Network	Phase I
TMC278LA	Non-nucleoside reverse transcriptase inhibitor, long-acting injectable formulation	St Stephens AIDS Trust	Phase I
UC-781	Reverse transcriptase inhibitor	Biosyn	Phase I

Preexposure Prophylaxis (PrEP)

The May 10, 2012, FDA Antiviral Drugs Advisory Committee meeting reviewed the available data on Truvada for PrEP at extraordinary length, and a webcast of the entire proceedings can be viewed online.[39] FDA briefing documents[40] and all the slide presentations from the meeting are also available.[41] The committee pored over the results of multiple trials; the two providing evidence of efficacy were iPrEx, conducted among 2,470 MSM and 29 transgender women at high risk of HIV infection, and Partners PrEP, which recruited 4,758 serodiscordant heterosexual couples. In the former trial, overall efficacy was 42% (95% confidence interval, 18–60%);[42] in the latter it was 75% (95%CI, 55–87%).[43] Adherence emerged as a key variable, with estimated efficacy being far higher among individuals with measurable drug levels: in a substudy of iPrEx, the estimated relative reduction in risk was 87.5% (95%CI, 66–95%) compared with placebo recipients;[44] in Partners PrEP it was 90% (95%CI, 58–98%).[45]

Additional studies considered by the FDA included the CDC TDF2 trial in 1,219 men and women in Botswana, in which there were a total of 33 HIV infections during follow-up: 9 among the individuals in the Truvada group and 24 among those assigned to placebo. The relative reduction in risk of HIV acquisition was 62% (95%CI, 21–83%).[46] The one trial that did not find evidence of protective efficacy was FEM-PrEP, which had enrolled 2,120 women in Kenya, Malawi, South Africa, and Tanzania when it was stopped by the DSMB in April 2011 because 56 infections had occurred: 33 in the Truvada arm, and 35 in placebo recipients. The reason for the lack of an effect is not fully clear, but it appears likely that adherence played a role; plasma drug levels were detectable in less than 50% of the Truvada recipients analyzed.[47]

Safety information for the FDA review came from the above-referenced trials and two other phase II studies of tenofovir alone that did not measure efficacy: CDC 4323, conducted in U.S. MSM, and FHI PrEP, which enrolled African women. Overall, no toxicities were identified that have not previously been documented in the context of Truvada's approved use as an HIV treatment. The primary concerns with the drug are kidney toxicity and decreased bone mineral density (BMD). No serious kidney toxicity occurred in any trial. There were seven discontinuations of Truvada in iPrEx due to elevated creatinine; all but one of the individuals restarted without recurrence. Two Truvada recipients in Partners PrEP discontinued due to decreased creatinine clearance that resolved after the drug was stopped. A BMD decrease of greater than 5% was documented in 14% of iPrEx participants assigned to Truvada compared to 6%

on placebo. A small but significant decrease in BMD also occurred among tenofovir recipients in the CDC 4323 study in comparison to those receiving placebo, and there were more reports of new onset back pain (13% vs. 6%). There were no significant differences in the incidence of new onset back pain in Partners PrEP. The occurrence of bone fractures did not differ significantly among groups in any study.

In terms of other adverse events that showed significant differences versus placebo, iPrEx reported nausea and unintended weight loss, while Partners PrEP found neutropenia occurred more frequently. Because Truvada is active against hepatitis B (HBV), one concern is that people with HBV who use PrEP might experience a flare in disease after the drug is stopped. There were 16 individuals with chronic or acute HBV in iPrEx, but no evidence of flares. Hepatic safety issues were also not seen among women with chronic HBV infection in the FHI PrEP trial.

Behavioral disinhibition or risk compensation—the idea that people might engage in activities that increase their risk of HIV infection as a result of receiving a prevention intervention—is a frequently cited bugbear in discussions about PrEP. It was not seen in any of the trials. The potential for individuals on PrEP to develop resistance to Truvada is another concern. In iPrEx, two individuals in the Truvada arm had undetected acute HIV infection at enrollment and developed resistance mutations (M184V and M184I) during the first four weeks of the trial. None of the participants who seroconverted during the trial showed evidence of drug resistance. Results were similar in Partners PrEP: three individuals in the Truvada arm had undiagnosed acute HIV infection at baseline, and one developed the M184V mutation by week 12. None of the individuals who became infected during the trial displayed drug resistance.

After reviewing the data, the Antiviral Drugs Advisory Committee delivered their votes, strongly supporting approval of Truvada for MSM and serodiscordant couples, while rendering a more equivocal verdict on the broader population of people at risk for HIV infection. The FDA's decision on whether to approve a prevention indication for Truvada is due to be announced by September 14, 2012. The decision has been delayed by negotiations between the FDA and the manufacturer, Gilead Sciences, regarding what is called a Risk Evaluation and Mitigation Strategy (REMS) that will be required to accompany prescriptions of the drug for prevention. A REMS can comprise multiple components, such as educational guides and health care provider training plans, intended to ensure that the drug is used correctly.

In anticipation of approval, multiple demonstration projects in different populations at high risk of HIV infection are in the beginning stages. Researchers are also considering the potential impact of PrEP on trials of other biomedical preventions: the HVTN and the Microbicide Trials Network (MTN) are to launch a joint study that will evaluate the potential interactions between a DNA/NYVAC prime-boost vaccine and oral or topical PrEP.[48]

One new PrEP agent that is entering a clinical trial—jointly sponsored by the HIV Prevention Trials Network (HPTN) and the AIDS Clinical Trials Group (ACTG)—is the CCR5 inhibitor maraviroc.[49] The study intends to enroll 400 HIV-negative MSM along with a cohort of 200 women, and will primarily assess safety and tolerability of maraviroc, given alone or in combination with emtricitabine or tenofovir.

Two trials are exploring intermittent use of PrEP. The HPTN is conducting the ADAPT study (Alternative Dosing to Augment PrEP Tablet-Taking, also known as HPTN 067) which is comparing different Truvada dosing schemes in 180 MSM and 180 heterosexual women at high risk of acquiring HIV infection. The trial is not of sufficient size to evaluate efficacy, but will assess tolerance, acceptability, and drug levels. In France, the ANRS is sponsoring IPERGAY, which is recruiting 300 MSM for an initial pilot phase. The schema involves taking two doses of Truvada (or placebo) within 24 hours prior to sexual activity, one dose every 24 hours during the period of sexual activity, and one dose 24 hours afterward. Depending on the results of the pilot phase, the trial may expand to enroll an additional 1,600 MSM.[50]

Microbicides

The major news in the microbicide field is the recent launch of The Ring Study (also known as IPM 027), a large phase III efficacy trial of the antiretroviral dapivirine, delivered via a vaginal ring. A total of 1,650 women will be enrolled at sites in South Africa, Rwanda, and Malawi. Developed and sponsored by the IPM, the dapivirine ring delivers drug for a four-week period before it needs replacing, potentially providing women with a convenient and discrete prevention method that is entirely under their control. A second complementary phase III trial of the approach, sponsored by the MTN and named the ASPIRE study, is due to start soon. ASPIRE will recruit 3,476 women from sites in Malawi, South Africa, Uganda, Zambia, and Zimbabwe.

The IPM has received funding from USAID to further develop the dapivirine ring with the aim of creating a modified version that can deliver drug for 60 days in combination with a contraceptive. Rings that deliver maraviroc alone or combined with dapivirine are also being studied in phase I trials.

Tenofovir gel, which reduced risk of HIV acquisition by 39% in the CAPRISA 004 study, is now being tested again in South Africa in a larger efficacy trial named FACTS 001. The goal is to enroll at least 2,200 women and obtain a definitive answer as to whether the approach works. A rectal formulation of tenofovir gel is also in development, after a safety study evaluating rectal application of the vaginal version revealed that it caused a surfeit of unpleasant gastrointestinal side effects.[51] Early results with the rectal formulation suggest it is far better tolerated,[52] and additional trials are imminent.

TABLE 3. Research Toward a Cure 2012

Clinical Trial	ClinicalTrials.gov Identifier(s)	Manufacturer/Sponsor(s)
ACE Inhibitors to Decrease Lymphoid Fibrosis in Antiretroviral-Treated, HIV-infected Patients: A Pilot Study	NCT01535235	University of California, San Francisco (UCSF)/amfAR
Allogeneic Transplant in HIV Patients (with chemotherapy-sensitive hematological malignancies and coincident HIV-infection) (BMT CTN 0903)	NCT01410344	National Heart, Lung, and Blood Institute (NHLBI)/ National Cancer Institute (NCI)/Blood and Marrow Transplant Clinical Trials Network
Alpha interferon intensification	NCT01295515	NIAID
Autologous T-cells Genetically Modified at the CCR5 Gene by Zinc Finger Nucleases SB-728 for HIV	NCT01543152 (with cyclophosphamide) NCT01044654 NCT00842634 (closed to enrollment) NCT01252641 (closed to enrollment)	Sangamo BioSciences
disulfiram (Antabuse)	NCT01286259 (closed to enrollment)	UCSF/The Johns Hopkins University
IL-7, DNA/Ad5 HIV vaccine, ART intensification	NCT01019551 (closed to enrollment) NCT00976404 (closed to enrollment)	Cytheris/Vical/GenVec, NIH Vaccine Research Center/ Objectif Recherche VACcins Sida (ORVACS)
vorinostat (SAHA)	NCT01319383 NCT01365065	Merck/University of North Carolina at Chapel Hill/ NIAID/Bayside Health

Cure research has become increasingly high-profile over the past year, but relatively few new clinical trials have been initiated. When evaluating the research portfolio, however, it is important to appreciate that the field is awash in definitional uncertainty. For example, the recent evidence suggesting therapeutic HIV vaccines have an important role to play means that, technically, all studies of these approaches could be considered cure research. Certainly, manufacturers of therapeutic vaccines have been quick to cite the goal of achieving a functional cure—control of HIV replication in the absence of ART—as pertinent to their products. For the purposes of this section of the *Pipeline*, we have focused on trials that make specific reference to assessing the impact of an intervention on the latent HIV reservoir, or that are connected to the CCR5 abrogation strategy that appears to have been central to the cure achieved in Timothy Brown.

New studies include an evaluation of whether angiotensin converting enzyme (ACE) inhibitors can reduce scarring damage to the lymph nodes (fibrosis) in HIV infection, and thereby also reduce the HIV reservoir. Lymph node fibrosis has been shown to progressively worsen during untreated HIV infection,[53] and can persist and limit CD4 T-cell recovery after ART initiation.[54]

Under the leadership of Richard Ambinder at the Johns Hopkins University and Joseph Alvarnas at the City of Hope National Medical Center, the Blood and Marrow Transplant Clinical Trials Network has opened a trial for HIV-positive individuals with chemotherapy-sensitive hematologic malignancies that will attempt to identify stem cell transplant donors homozygous for the CCR5-Delta32 mutation. The goal is to try to duplicate the results obtained in Timothy Brown. A company named StemCyte is pursuing the same goal with a slightly different approach: stem cell transplants derived from cord blood. At a recent conference, Lawrence Getz from StemCyte reported that so far they have identified around 102 cord blood donors homozygous for CCR5-Delta32 out of around 17,000 tested. Although there is no formal trial, an individual with HIV in the Netherlands has recently received such a transplant as part of treatment for a hematologic malignancy, and the same procedure is about to be used in a similar case in Madrid.[55]

By pairing zinc finger proteins with enzymes called nucleases that can break up DNA, the experimental therapy being developed by Sangamo BioSciences—SB-728—disrupts the CCR5 gene and thus prevents expression of the CCR5 coreceptor on modified cells. In current trials, CD4 T cells are extracted from participants via apheresis, subjected to the zinc finger nuclease procedure in the laboratory, and then expanded in number and reinfused. Early trial results were available last year, but there have been several developments since that time.

Most intriguingly, one study involves a 12-week interruption of ART, and participants have shown evidence of viral load declines prior to ART reinitiation. Analyses of the data revealed a significant inverse correlation between the number of detectable gene-modified CD4 T cells and viral-load levels, indicating an antiviral effect.[56] One notable individual showed a viral-load reduction to undetectable levels prior to restarting ART, and it turned out that this person was heterozygous for the CCR5-Delta32 mutation; because this renders one of the two CCR5 genes present in each cell defective, there was less work for Sangamo's therapy to do, and the levels of modified cells were much higher. In an attempt to duplicate and extend these findings, Sangamo is now specifically recruiting individuals heterozygous for CCR5-Delta32 into an expanded trial. Another new study is evaluating whether a brief period of immune-suppressive treatment with the drug cyclophosphamide can increase the expansion of gene-modified CD4 T cells after infusion (essentially by making more "space" for them to flourish).

The leading strategy for awakening the latent HIV reservoir involves the use of a class of anticancer drugs called histone deacetylase (HDAC) inhibitors. Numerous in vitro studies have shown that these drugs can stimulate HIV RNA expression by latently infected CD4 T cells.[57] Toward the end of 2011, David Margolis from the University of North Carolina presented the first human data on the approach, and he delivered further updates at the 2012 CROI[58] and Keystone[59] meetings.

Margolis is conducting a phase I/II trial of the HDAC inhibitor vorinostat (also known as SAHA, trade name Zolinza) in people with HIV on long-term ART with suppressed viral loads. The protocol schema is complex, partly due to safety concerns. The anti-latency effect of the drug is being measured 4–6 hours after a single 400 mg dose. Because latently infected CD4 T cells are very rare, large numbers of cells (approximately 4 billion) are extracted from each participant at baseline and after receipt of the drug. The samples are divided into pools of around 1 million purified resting CD4 T cells each, ending up with 24–36 pools per person at each time point. HIV RNA expression is then measured in each pool, and averaged to arrive at a median level for each individual, before and after vorinostat treatment. At the Keystone conference, Margolis was able to report results from seven participants, all of whom showed an increase of HIV RNA expression. The median increase for the entire study population compared to baseline was 5.2-fold. Margolis believes this is evidence that the drug is working as hoped.

In Australia, Sharon Lewin from Monash University is undertaking a trial of vorinostat that involves 14 days of treatment as opposed to a single dose.

Data on the effect on the latent HIV reservoir are not yet available, but Lewin was able to present preliminary safety results at CROI.[60] Grade 1 and 2 adverse events were common, including lethargy, nausea, vomiting, diarrhea, thrombocytopenia (decreased platelet counts), and increased levels of the enzyme alkaline phosphatase; all resolved after the 14-day dosing period. This panoply of side effects is consistent with what is known from the use of vorinostat in cancer, and illustrates why HDAC inhibitors are being considered only for short-term use in cure-related research.

An important question pertaining to latency-reversing approaches is whether successful induction of HIV RNA expression in latently infected CD4 T cells will be sufficient to cause cell death. Two studies debuted in 2012 suggest that the answer to this question is no. The laboratory of Tae-Wook Chun at NIAID explored the issue using in vitro assays and found that HDAC inhibitors did not cause latently infected CD4 T cells to die by virus-induced cytopathic effects.[61] Liang Shan from Robert Siliciano's research group at the Johns Hopkins University obtained similar results but found that, after exposure to HDAC inhibitors, the CD4 T cells could be eliminated by functional HIV-specific CD8 T cells. However, while HIV-specific CD8 T cells sampled from elite controllers performed this task with gusto, the same was not true for most individuals with chronic infection. In order to persuade HIV-specific CD8 T cells from the latter group to work, they needed to be stimulated with HIV antigens prior to being mixed with the latently infected cells. Shan and colleagues conclude that therapeutic HIV vaccines will need to be combined with anti-latency strategies if elimination of the latent reservoir is to be achieved.[62]

Disulfiram (Antabuse) is an approved drug used to treat alcoholism that has shown anti-latency potential in a laboratory study.[63] Preliminary results of a small phase I trial were presented at the 2012 CROI but did not provide clear evidence of an effect.[64] There was a suggestion of an increase in HIV RNA expression very soon after dosing; additional work is now being performed to assess whether this observation was real or artefactual.

On the cure-research funding front, in July 2011 NIAID announced the award of three multimillion-dollar five-year grants under the aegis of the Martin Delaney Collaboratory, a program named in memory of the longtime AIDS activist and founder of Project Inform, who died in 2009. Grantees include:

- David Margolis at the University of North Carolina at Chapel Hill, who is leading the largest of the groups, consisting of 15 scientific projects at nine different academic research centers throughout the U.S. Merck Research Laboratories is a key part of this team, but will

not be receiving funding from the National Institutes of Health (NIH). The major goals are to improve the understanding of HIV persistence despite antiretroviral therapy and to develop therapies to target and eliminate viral reservoirs.

- A triumvirate of principal investigators—Steve Deeks and Mike McCune at University of California, San Francisco, and Rafick-Pierre Sékaly at the Vaccine and Gene Therapy Institute of Florida—who are overseeing seven projects aiming at determining where HIV reservoirs are located in the body and how they are created and maintained, with the ultimate goal of developing therapies that can eliminate reservoirs without causing excessive immune activation.

- Keith R. Jerome and Hans-Peter Kiem at the Fred Hutchinson Cancer Research Center, who are embarking on five projects, including a collaboration with Sangamo BioSciences on the use of hematopoietic cell transplants to create HIV-resistant immune cells (Kiem has developed a macaque model for evaluating this type of approach). Jerome is also pursuing the use of proteins called endonucleases to excise the HIV genome from latently infected cells.[65]

A glimpse at Hans-Peter Kiem's preclinical work was offered earlier this year when he presented results of a small macaque experiment that introduced a gene encoding an anti-HIV fusion inhibitor into stem cells and transplanted them into the animals, giving rise to a population of CD4 T cells resistant to infection.[66] Although only a minority of the total CD4 T-cell population displayed evidence of gene modification, the macaques exerted an unusual degree of control over a SHIV challenge and did not progress to simian AIDS. The researchers believe that gene-modified virus-specific CD4 T cells likely mediated the effect. In future experiments, they plan to study whether immunization with SHIV antigens after transplantation can enhance the numbers of gene-modified virus-specific CD4 T cells and further improve control of viral replication.[67] Depending on the outcome, it may open another door for therapeutic vaccines—in this case to be used in combination with gene therapy approaches.

Defining a Cure

In addition to the uncertainty regarding exactly what constitutes cure research, a recent unfortunate outburst of controversy has highlighted the fact that there is no consensus as to exactly how a cure is defined. The situation arose after a presentation by Steven Yukl from UCSF describing the results

of intensive studies searching for HIV in Timothy Brown. Almost all the results were negative, including tests for infectious virus in vast numbers of cells (approximately 9 billion). No viral RNA or DNA could be found in peripheral blood mononuclear cells (PBMCs) or cerebrospinal fluid (CSF). But trace amounts of HIV RNA were detected in plasma by two laboratories, and another laboratory obtained positive results for HIV DNA in a minority of rectal samples. Genetic sequencing results were suggestive of contamination in at least one instance (a common problem with the assays used). The researchers involved in the study were careful to note that the results do not mean that Timothy Brown isn't cured, but rather illustrate the difficulty of formally distinguishing between a sterilizing cure—in which all virus is eradicated—and a functional cure, the term used to refer to the scenario where any residual HIV is controlled in the absence of any treatment. This did not prevent a barrage of wild speculation about the results from one scientist, and the appearance of a slew of press stories—of varying accuracy—on the subject. It is likely that researchers will be wrestling with the question of how best to define a cure for some time.

Immune-Based and Gene Therapies, and Therapeutic Vaccines

As touched on in the preceding section, the cure research renaissance has opened up new opportunities for these black sheep of the therapeutic pipeline. Until quite recently, the increasing effectiveness and tolerability of ART, along with the new appreciation of the inflammatory dangers posed by uncontrolled HIV replication, had led to a waning of interest in alternative approaches. Although most of the candidates in these categories predate the renewed interest in curing HIV, it is likely that many—particularly therapeutic vaccines—are destined to be studied in that context rather than as an adjunct to ART.

The exceptions are therapies that aim to address the immune dysfunction that can persist in some HIV-positive individuals despite suppression of viral replication. Currently, the cytokine IL-7 appears to be the only immune-based therapy with any prospect of being evaluated for clinical benefit in this setting. A new study of IL-7 presented at the 2012 CROI may bolster the case for further studies, as it found that in addition to increasing CD4 and CD8 T-cell numbers in peripheral blood, administration of the cytokine to HIV-positive individuals on ART boosted CD4 T-cell levels in the gut and reduced soluble CD14 and D-Dimer, two inflammation-associated biomarkers that have been linked to mortality.[68]

TABLE 4. Immune-Based and Gene Therapy Pipeline 2012

Agent	Class/Type	Manufacturer/ Sponsor(s)	Status
maraviroc (Selzentry)	CCR5 inhibitor	Pfizer	Phase IV
mesalamine (5-aminosalicylic acid)	Oral anti-inflammatory drug approved for the treatment of inflammatory bowel disease	UCSF/Salix Pharmaceuticals	Phase IV
chloroquine phosphate	Antimalarial, anti-inflammatory	NIAID/ACTG	Phase II
etoricoxib	Cox-2 inhibitor, anti-inflammatory	Oslo University Hospital	Phase II
interleukin-7 (CYT 107)	Cytokine	Cytheris	Phase II
Lexgenleucel-T (formerly referred to as VRX496)	Lentiviral vector encoding antiretroviral antisense, introduced into CD4 T cells ex vivo	VIRxSYS	Phase II
Umbilical Cord Mesenchymal Stem Cells (UC-MSC)	Adult stem cells originating from the mesenchymal and connective tissues	Beijing 302 Hospital	Phase I//II
Gene Transfer for HIV Using Autologous T Cells	Infusions of autologous CD4 T cells modified with by a lentivirus vector encoding 3 forms of anti-HIV RNA: pHIV7-shI-TAR-CCR5RZ	City of Hope Medical Center/ Benitec Ltd	Phase I
HLA-B*57 cell transfer	Cell infusion	NIH Clinical Center	Phase I
hydroxychloroquine	Antimalarial, antirheumatic, anti-inflammatory	St Stephens AIDS Trust	Phase I
M87o	Entry inhibitor gene encoded by a lentiviral vector, introduced into CD4 T cells ex vivo	EUFETS AG	Phase I
Redirected high affinity Gag-specific autologous T cells for HIV gene therapy	Gene therapy that introduces an HIV-specific T-cell receptor into CD8 T cells and reinfuses them	University of Pennsylvania	Phase I
SB-728-T	Autologous T-cells genetically modified at the CCR5 gene by zinc finger nucleases	Sangamo BioSciences	Phase I

TABLE 5. Therapeutic Vaccines Pipeline 2012

Agent	Class/Type	Manufacturer/Sponsor(s)	Status
Vacc-4x	Synthetic peptides from the HIV-1 Gag p24 protein + adjuvant	Bionor Immuno	Phase IIb
AGS-004	Mature dendritic cells electroporated with autologous HIV-1 RNA and CD40L RNA	Argos Therapeutics	Phase II
DCV-2	Autologous myeloid dendritic cells pulsed ex vivo with high doses of inactivated autologous HIV-1	University of Barcelona	Phase II
DermaVir patch (LC002)	DNA expressing all HIV proteins except integrase formulated to a mannosilated particle to target antigen-presenting cells	Genetic Immunity	Phase II
FIT-06, GTU-MultiHIV vaccine	DNA vaccine encoding complete sequences of HIV-1 clade B Rev, Nef, Tat, and p17/p24 proteins, and T-cell epitopes from Pol and Env proteins	FIT Biotech	Phase II
GSK HIV vaccine 732462	p24-RT-Nef-p17 fusion protein in proprietary adjuvant AS01B	GlaxoSmithKline	Phase II
HIV-1 Tat vaccine	Tat protein vaccine	National AIDS Center at the Istituto Superiore di Sanità, Rome	Phase II
VAC-3S	3S peptide from gp41	InnaVirVax	Phase I/IIa
Autologous HIV-1 ApB DC vaccine	Autologous dendritic cells pulsed with autologous, inactivated HIV–infected apoptotic cells	University of Pittsburgh	Phase I/II
DNA/MVA	DNA vaccine and an MVA vector encoding HIV-1 Gag and multiple CTL epitopes	Cobra Pharmaceuticals/ IDT/University of Oxford/ U.K. Medical Research Council	Phase I/II

TUTI-16	Synthetic HIV-1 Tat epitope vaccine	Thymon, LLC	Phase I/II
Vacc-C5	Peptides from the C5 region of gp120	Bionor Pharma	Phase I/II
AFO-18	18 peptides representing 15 CD8 T-cell epitopes and 3 CD4 T-cell epitopes from HIV-1 in an adjuvant (CAF01)	Statens Serum Institut/ Ministry of the Interior and Health, Denmark/European and Developing Countries Clinical Trials Partnership	Phase I
Autologous dendritic cell HIV vaccine	Autologous dendritic cells pulsed with conserved HIV-derived peptide	University of Pittsburgh	Phase I
DC vaccine	Autologous dendritic cells generated using GM-CSF and interferon alpha, loaded with lipopeptides and activated with lipopolysaccharide	Baylor University/ANRS	Phase I
HIV-v	Lyophilised mixture of polypeptide T-cell epitope sequences	Seek	Phase I
HIVAX	Replication-defective HIV-1 vector pseudotyped with VSV-G envelope	GeneCure Biotechnologies	Phase I
MAG-pDNA vaccine, GENEVAX, TriGrid	Multiantigen DNA vaccine comprising the Env, Gag, Pol, Nef, Tat, and Vif proteins of HIV-1 and GENEVAX, interleukin-12 (IL-12) pDNA adjuvant, delivered using the electroporation-based TriGrid delivery system	ACTG/NIAID/ Profectus Biosciences, Inc./ Ichor Medical Systems	Phase I
mRNA-transfected autologous dendritic cells	Dendritic cells transfected with vectors encoding consensus HIV-1 Gag and Nef sequences	Massachusetts General Hospital	Phase I
MVA HIV-B	MVA vector including HIV-1 Bx08 gp120 and HIV-1 IIIB Gag, Pol, and Nef	Hospital Clinic of Barcelona	Phase I
MVA.HIVconsv	MVA vector	University of Oxford/ Medical Research Council	Phase I

PENNVAX-B (Gag, Pol, Env) + electroporation	DNA vaccine encoding Gag, Pol, and Env genes of HIV-1 + electroporation	Inovio Pharmaceuticals/ University of Pennsylvania	Phase I
PENNVAX-B, GENEVAX IL-12-4532, pIL15EAM	DNA vaccine including HIV-1 Env, Gag, and Pol, with GENEVAX IL-12 and IL-15 adjuvants	University of Pennsylvania/ Drexel University	Phase I
pGA2/JS7 DNA MVA/HIV62B	Prime: DNA vaccine Boost: MVA vector Both including Gag, Pol, and Env genes from HIV-1 clade B	GeoVax, Inc./AIDS Research Consortium of Atlanta/University of Alabama at Birmingham/ AIDS Research Alliance	Phase I
SAV001-H	Whole-killed HIV-1 vaccine	Sumagen	Phase I

A number of developments have occurred in the therapeutic HIV vaccine field over the past year. While there have been no earth-shattering breakthroughs, two studies have added to prior hints that HIV-specific immunity can be modulated sufficiently to reduce viral load, even though the effects have generally been meager and transient. In one case, a DNA vaccine developed by FIT Biotech appeared to make a very mild dent in viral load levels among individuals for whom ART was not yet indicated.[69] A post hoc analysis from a phase II trial of Vacc-4x, a peptide-based vaccine developed by Bionor Pharma also suggested a reduction in viral load during an ART interruption.[70] While it is hard to envision these results leading to therapeutic vaccines replacing ART, they do offer reasons to hope that in cure research—where the aim is to deal with small numbers of infected cells in combination with other approaches—the enhancement in HIV-specific immunity might be able to make a crucial contribution.

There are several newcomers to the therapeutic HIV vaccine pipeline. Jonas Salk's whole-killed candidate Remune is long gone, but a similar vaccine developed by Sumagen is entering phase I. Although they are often derided, killed vaccines can be highly effective at inducing CD4 T-cell responses, and recent data indicate that HIV-specific CD4 T cells can play an important role in controlling viral load.[71] HIVAX is an unusual contender developed by GeneCure Biotechnologies; unlike most vaccines, it is based on a nearly entire replication-defective HIV genome, meaning it encodes almost all viral antigens.

Two candidates are not designed to enhance HIV-specific immunity, but rather to induce antibody responses that may reduce the ability of the virus to

cause harmful effects (such as CD4 T-cell apoptosis and immune activation). VAC-3S aims to induce antibodies against an epitope from the HIV gp41 protein, based on the idea that this will prevent CD4 T cells being nudged into apoptosis by natural killer cells.[72] Bionor Pharma is developing Vacc-C5 as a complement to their Vacc-4x construct. The vaccine is based on the C5 protein from gp120, and the rationale is that antibodies against this target may reduce immune activation.[73]

Conclusion

To the extent that a theme can be identified in the disparate pipelines covered in this chapter, it is: combine, combine, combine. The imminent arrival of PrEP is not viewed by anyone as a panacea for prevention, but rather a step toward the availability of a smorgasbord of options that can be mixed and matched for maximum convenience and effectiveness, depending on an individual's situation. HIV vaccines have finally ditched the dichotomy of cellular versus humoral immunity and, absorbing the lessons of RV144, embraced the marriage of the two. Cure research, once viewed as the domain of monomaniacal virologists, finds itself calling for immunologic contributions from therapeutic vaccines. Hopefully, the tools we need to prevent and cure HIV infection will soon emerge from this dizzying search for synergies.

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HEPATITIS C DRUG DEVELOPMENT GOES FROM PONY RIDE TO ROCKET LAUNCH

By Tracy Swan and Karyn Kaplan

Dedicated to Michael Carden
A fabulous, kind, brilliant, and hilarious friend and colleague
1971–2012

Special thanks to Jules Levin

Introduction

Hepatitis C virus (HCV) infection is curable, although it still kills more than 365,000 people each year.[1] Successful treatment reduces the risk of liver-related illness and death, even in people who have cirrhosis,[2–5] but pegylated interferon—the backbone of HCV treatment—is also the major obstacle to treatment access, delivery, uptake, and completion.

Fortunately, a revolution in HCV drug development is under way: proof of concept for safe and effective all-oral, interferon-free regimens has been established, and dozens of drugs from different classes are in development.

Treatment advances are long overdue for an estimated 160 million people with chronic hepatitis C.[6] Although HCV progresses slowly, liver damage develops exponentially once serious liver scarring—called bridging fibrosis—occurs; almost 10% of this group will progress to cirrhosis each year.[7] People with cirrhosis are vulnerable to liver failure and hepatocellular carcinoma (HCC; liver cancer). By 2007, more people in the United States were dying from HCV complications than from HIV/AIDS.[8]

In mid-2011, approval of the first hepatitis C protease inhibitors—Merck's boceprevir (Victrelis) and Vertex's telaprevir (Incivek/Incivo)—marked the beginning of the direct-acting antiviral (DAA) era. Although both drugs must be used with pegylated interferon (PEG-IFN) and ribavirin (RBV), their use increases the likelihood of being cured, and offers the possibility of shortened treatment.[9–13]

In real life, enduring and administering treatment with an HCV protease inhibitor–based regimen has turned out to be more difficult than patients and clinicians were led to expect based on data from clinical trials. Treatment-experienced people with advanced liver disease face harsh—even life-threatening—side effects. They require vigilant monitoring by experienced physicians. Serious adverse events have been reported in 30% to 51% of people with cirrhosis, versus 9% to 14% among participants in phase III clinical trials.[14] The shortage of qualified and willing treaters—who must follow complex drug- and patient-specific treatment algorithms—combined with rumors of unfamiliar and worse-than-expected side effects, high prices, and anticipation of better drugs, have circumscribed HCV treatment uptake in the United States and Europe.

The longing for simple, easy-to-tolerate, interferon-free regimens is fed by industry hype. The current treatment paradigm—which involves consideration of host and viral genotype, HCV subtype, liver histology, treatment history, and response to treatment at designated time points—will become less complex in the coming years, hopefully evolving into DAA regimens that will cure everyone.

Who's Special?

> *With all of this exciting information, there is nothing exciting for them.*
>
> —Gloria Searson, MSW
> Founding Director, Coalition for Positive Empowerment (COPE)

People with poor prognostic factors and greater need for treatment are often lumped together as "special populations," which makes it easier to exclude them from registration trials. Instead, pharmaceutical companies design trials for people who are easier to treat but do not reflect the demographics of the HCV epidemic. When drugs are approved, information on their safety and efficacy in African Americans, Latinos and Latinas, people with common comorbidities such as HIV and bleeding disorders, people over 65 years of age, and people with cirrhosis is often limited. Underrepresentation or outright exclusion of current and former drug users and people on medication-assisted treatment with methadone or buprenorphine is a chronic problem—which persists despite ample evidence that they can be successfully treated.[15–20]

Now that it is possible to treat HCV without interferon, it is inexcusable to delay clinical trials in people with urgent need for them. Nonetheless, people with decompensated cirrhosis as well as transplant candidates and recipients are

excluded from pre-approval trials despite pressure from activists, regulators, and desperate patients and their physicians.

Resistance

There is no consensus on whether there are clinical consequences associated with HCV drug resistance. Some experts are convinced that it will limit future treatment options, while others tend to dismiss it, citing both the development of many new and potent DAAs from different classes, and studies documenting reversion to wild-type virus over time.

It has become clear that HCV treatment is more likely to fail when preexisting resistance is compounded by poor interferon sensitivity and lower drug concentrations.[21,22] In contrast, pretreatment drug resistance does not always preclude successful treatment in people who are sensitive to interferon.[21–23] More data are needed, but in the meantime, pretreatment IL28B testing and HCV subtyping may help to identify people who are vulnerable to resistance-associated treatment failure.

Drug-Drug Interactions

Drug-drug interactions can lower DAA concentrations to subtherapeutic levels, leading to drug resistance and treatment failure, or increase drug concentrations, leading to worsened side effects and drug toxicity.

Treating HCV in HIV/HCV-coinfected people is complicated by drug-drug interactions with antiretroviral agents and other medications, especially in people over 50 years of age, since polypharmacy (use of multiple medications) is more common in older HIV-positive people (see Table 4. Drug-Drug Interactions between HCV DAAs and HIV Antiretroviral Agents, page 162).[24,25]

Since injection drug use with unsterilized equipment is a major mode of transmission for HCV, many people with hepatitis C are on substitution therapy with methadone or buprenorphine. Transplant recipients need immunosuppressive therapy. Type 2 diabetes and psychiatric disorders are common among people with hepatitis C. Drug-drug interaction studies should be performed to determine whether methadone, buprenorphine, immunosuppressants, insulin-sensitizing agents, statins (to lower cholesterol), psychotropic medications, and antiretroviral agents can safely be used during HCV treatment. Serious clinical consequences of uncharacterized drug-drug interactions include overdose, graft rejection, muscle weakness, and rhabdomyolysis (muscle damage that can lead to kidney failure).[26]

Up-to-date and comprehensive information on DAA drug interactions is available from the University of Liverpool at http://www.hep-druginteractions.org/.

DAAs by Class

Nucleosides and Nucleotide Polymerase Inhibitors

Nucleosides and nucleotide polymerase inhibitors are a therapeutic backbone for interferon-free regimens.

PSI-7977, the nucleotide furthest along in development, has been hailed as a wonder drug for its potency, high resistance barrier, and activity across HCV genotypes, favorable side-effect profile, and once-daily dosing. Results from small phase II trials supported the notion that PSI-7977 could cure everyone, possibly without pegylated interferon, and perhaps even as a monotherapy. On November 21, 2011, Gilead announced its plan to purchase Pharmasset for US$11 billion dollars; the sale went through in early 2012. Thus, PSI-7977 became GS-7977.

Since then, it has become clear that the wonder drug may need some help if it is indeed to be a cure-all. High relapse rates in people treated with monotherapy, prior null responders with HCV genotype 1, and treatment-experienced people with HCV genotypes 2 and 3 indicate the need for longer therapy and, possibly, other DAAs.

NS5a Inhibitors

NS5a inhibitors are active against all HCV genotypes, and they are potent, despite a low barrier to drug resistance. This class of drugs is moving into a co-anchor role in interferon-free regimens based on daclatasvir's large safety database, favorable side-effect profile, once-daily dosing, and performance with other DAAs (GS-7977 and asunaprevir). Many drugs in this class feature once-daily dosing and pan-genotypic activity. Next-generation NS5a inhibitors are likely to have a higher resistance barrier.

HCV Protease Inhibitors

HCV protease inhibitors were the first class of DAAs to be approved. Subsequent versions will be optimized. The second batch of protease inhibitors is now in phase III; they will offer once-daily (versus thrice-daily) dosing, simpler treatment algorithms, and the prospect of greater efficacy. Tolerability may be better than that of first-generation protease inhibitors, despite side effects such as photosensitivity, abnormal elevations in bilirubin (a yellowish fluid created when the liver breaks down red blood cells), nausea, and vomiting. The next generation of protease inhibitors may be active against multiple genotypes and drug-resistant virus.

Non-Nucleoside Polymerase Inhibitors

Enthusiasm for this class of drugs has increased in the wake of its contribution to interferon-free regimens. Non-nucleosides generally have a low resistance barrier and are active only against genotype 1, but it may be possible to combine drugs from this class, as they target different sites (thumb- versus palm region of the HCV genetic structure).

TABLE 1. Direct-Acting Antivirals in Phase II and Phase III

(For more detailed listing of current trials for each drug, see page 168.)

Agent	Dosing	Sponsor	Status
Nucleoside/nucleotide polymerase inhibitors			
GS-7977 (formerly PSI-7977)	Once-daily	Gilead Sciences	Phase III
BMS-986094 (formerly INX-189)	Once-daily	Bristol-Myers Squibb	Phase II
IDX-184	Once-daily	Idenix Pharmaceuticals	Phase II
mericitabine (RG7128)	Twice-daily	Hoffmann-La Roche	Phase II
NS5a inhibitors			
daclatasvir (BMS-790052)	Once-daily	Bristol-Myers Squibb	Phase III
ABT-267	Once-daily	Abbott Laboratories	Phase II
GS-5885	Once-daily	Gilead Sciences	Phase II
GSK2336805	Once-daily	GlaxoSmithKline	Phase II
IDX-719	Once-daily	Idenix Pharmaceuticals	Phase I/II
Protease inhibitors			
asunaprevir (BMS-650032)	Twice-daily	Bristol-Myers Squibb	Phase III
BI 201335	Once-daily	Boehringer Ingelheim	Phase III
simeprevir (TMC435)	Once-daily	Janssen/Tibotec/Medivir	Phase III
vaniprevir (MK-7009)	Twice-daily	Merck	Phase III
ABT-450/r (ritonavir-boosted)	Once-daily	Abbott Laboratories	Phase II
ACH-1625	Once-daily	Achillion Pharmaceuticals	Phase II
danoprevir/r (RG7227) (ritonavir-boosted)	Twice-daily	Hoffmann-La Roche/Genentech	Phase II
GS-9256	Twice-daily	Gilead Sciences	Phase II
GS-9451	Once-daily	Gilead Sciences	Phase II
MK-5172	Once-daily	Merck	Phase II
Non-nucleoside polymerase inhibitors			
ABT-072	Once-daily	Abbott Laboratories	Phase II
ABT-333	Twice-daily	Abbott Laboratories	Phase II
BI 207127	Twice-daily	Boehringer Ingelheim	Phase II
BMS-791325	Twice-daily	Bristol-Myers Squibb	Phase II
setrobuvir (ANA598)	Twice-daily	Anadys/Hoffmann-La Roche	Phase II
tegobuvir (GS-9190)	Twice-daily	Gilead Sciences	Phase II
VX-222 (formerly VCH-222)	Twice-daily	Vertex Pharmaceuticals	Phase II

THE NEXT GENERATION

Fierce competition for the most effective and most tolerable regimen—with the shortest treatment duration—continues, with the focus on HCV genotype 1. The next drugs likely to be approved to treat hepatitis C are once-daily protease inhibitors (TMC435 and BI 201335). Both are being developed with pegylated interferon and ribavirin (PEG-IFN/RBV), and with other DAAs in interferon-free trials.

Drugs from other classes are also moving closer to the clinic: daclatasvir, an NS5a inhibitor, and GS-7977, a nucleotide polymerase inhibitor, are in phase III. Data from these trials are important for informing and optimizing DAA use in interferon-free regimens.

Simeprevir (TMC435)

Janssen's once-daily HCV protease inhibitor, simeprevir, is currently in phase III trials.

PILLAR, a phase IIb trial in 368 treatment-naive people with HCV genotype 1, compared simeprevir dose (75 mg vs. 150 mg) and duration (12 vs. 24 weeks), in combination with PEG-IFN/RBV. Early responders were eligible for shortened treatment; otherwise, they continued on PEG-IFN/RBV for 48 weeks. Overall, the highest SVR rates (sustained virological response; HCV RNA becomes undetectable and remains undetectable for 24 weeks after treatment; regarded as a cure) and lowest relapse rates were seen with the 150 mg dose, especially with 24 weeks of triple therapy. In addition, SVR rates in the 150 mg dosing arms did not differ according to HCV subtype (genotype 1a or 1b), supporting use of the 150 mg dose in phase III studies.

Most participants (79–86%) were eligible for shortened treatment, forgoing the extra 24 weeks of PEG-IFN/RBV; and almost all early responders (93–96%) achieved SVR. As expected, the highest SVR rates were seen in people with the IL28B CC genotype (which is associated with interferon sensitivity and greater likelihood of SVR), whether or not they received simeprevir. In the IL28B CT and TT (harder-to-treat) groups, SVR was highest (78%) in the 150 mg dosing group, and lowest in the placebo group (50%). Oddly, SVR in the arm treated with PEG-IFN/RBV and placebo was 65%, higher than what has usually been reported.

Grade 3 or 4 adverse events occurred in 32% of the simeprevir arms, versus 35% of the placebo arm. Serious adverse events were twice as common in the placebo arm (13% vs. 6.5%), possibly due to shorter duration of PEG-IFN/RBV among most of the participants in the simeprevir groups. These events led to treatment discontinuation in 3.6% of the simeprevir groups, versus 5.2% in the placebo arm. The five most common adverse events among people treated with simeprevir were fatigue, flu-like symptoms, itching, headache, and nausea; the incidence of rash, anemia, and neutropenia (a decrease in white blood cells that fight off bacterial infections) did not differ significantly by treatment group. Transient elevations in bilirubin levels were seen in people who were treated with 150 mg of simeprevir; these elevations were attributed to blocked drug transporters (proteins that move drugs in and out of cells).[27]

ASPIRE, a phase IIb trial in prior relapsers, partial responders, and null responders with HCV genotype 1, looked at different doses (100 mg vs. 150 mg) and duration (12 vs. 24 vs. 48 weeks) of treatment with simeprevir with PEG-IFN/RBV. The best results were seen in the 150 mg dosing groups: 85% of prior relapsers, 75% of prior partial responders, and 51% of null responders achieved SVR. Although HCV subtype did not make a difference among relapsers, prior partial and null responders with HCV genotype 1a were less likely to be cured, as were people with more advanced liver damage; of note, 31% of prior null responders with cirrhosis were cured.[28]

SVR rates were similar in study participants (regardless of preexisting resistance) who received the 150 mg dose (vs. 100 mg). On-treatment viral breakthrough and posttreatment relapse rates were lower with the 150 mg dose (9% vs. 13% for breakthrough; 9% vs. 11% for relapse). After treatment, drug resistance was seen in 42 of 43 people who experienced breakthrough, and in 34 of 36 people who relapsed. People with HCV genotype 1a were more likely to have the R155K mutation by itself or with additional mutations, whereas people with HCV genotype 1b had the D168V mutation.[29]

Participants in the 150 mg arm had more grade 3 and 4 adverse events than those in the 100 mg or placebo arms (36% vs. 28% vs. 26%, respectively), and discontinuation rates were 9% (150 mg) versus 7% (100 mg) versus 5% (placebo). The most frequent adverse events—experienced by more than 25% of study participants—were headache, fatigue, flu-like symptoms, and itching. Other side effects included rash in 30%, 23%, and 18%, respectively; of note, severe rash was reported in 0.5% of participants treated with simeprevir, and photosensitivity in 2–6% of the simeprevir groups versus 2% of the placebo group. Laboratory abnormalities were similar across treatment groups, with the exception of mild, reversible elevations in bilirubin in simeprevir recipients.[28]

BI 201335

Boehringer Ingelheim's once-daily HCV protease inhibitor, BI 201335, has entered phase III.

SILEN-C1 was a four-arm phase II trial in 429 treatment-naive people with HCV genotype 1. Participants were assigned to treatment with 120 mg or 240 mg of BI 201335 (or placebo) once daily, plus PEG-IFN/RBV. The entire 120 mg dosing arm and half of the 240 mg dosing arm began treatment with a three-day PEG-IFN/RBV lead-in. In the 240 mg dosing arm, early responders were randomized to either stop treatment at 24 weeks or continue with a 24-week PEG-IFN/RBV "tail"; the remaining study participants took 120 mg of BI 201335 or placebo for 24 weeks, plus 48 weeks of PEG-IFN/RBV.

In the placebo arm, 56% achieved SVR, while SVR in the BI 201335 groups ranged from 71% to 83%. The highest rate of SVR occurred in the no-lead-in 240 mg arm. In the response-guided 240 mg arm, 87% of participants required only 24 weeks of treatment.

In people with the IL28B CC genotype, 100% of the 240 mg group and 82% of the placebo group achieved SVR. High-dose BI 201335 significantly increased cure rates in people with non-CC genotypes to 71%, versus 41% in the placebo arm. SVR did not differ significantly by HCV subtype (82% in genotype 1a vs. 84% in genotype 1b).

Severe adverse events were reported in 11.8% of those in the 120 mg BI 201335 arm, 12.8% to 15.9% in the 240 mg arms, and 4.2% in the placebo arm. These led to discontinuations in 4.4% of those in the 120 mg dosing arm, 5.4% to 11.6% in the 240 mg dosing arms, and 1.4% in the placebo arm. One death was reported in the placebo arm (the cause was not described). Discontinuations for rash, jaundice, and photosensitivity occurred only in the 240 mg dosing arms.[30]

In SILEN-C2, 288 partial- or null responders with HCV genotype 1 were randomized into three treatment arms: 240 mg of BI 201335 once daily, with or without a three-day PEG-IFN/RBV lead-in, or BI 201335 twice daily with a three-day PEG-IFN/RBV lead-in. After 24 weeks of triple therapy, early responders assigned in the once-daily lead-in group either stopped all treatment or continued with an additional 24 weeks of PEG-IFN/RBV. Everyone else stopped BI 201335 at week 24 and continued PEG-IFN/RBV until week 48.

SVR rates ranged from 27% (once-daily, with lead-in) to 31% (twice-daily, with lead-in) up to 41% (once-daily, no lead-in group). The highest SVR in partial responders was 50%; among null responders it was 35% (both in the once-daily, no lead-in group). Among early responders in the once-daily lead-in group, those treated for 48 weeks were significantly less likely to relapse (21% vs. 60%, respectively). Most treatment failures were due to breakthrough during triple therapy and relapse.

Adverse events that were >10% more frequent during treatment with BI 201335 included rash, jaundice (from BI 201335–associated bilirubin elevations), nausea, diarrhea, and vomiting. These usually occurred less often in the once-daily dosing arm. Severe adverse events were reported in 14% of the once-daily dosing arms, and 27% in the twice-daily dosing arm, leading to treatment discontinuation in 4% to 6% (once-daily) versus 23.2% (twice-daily). Rash accounted for 1.3% (once-daily) versus 14.5% (twice-daily) of treatment discontinuation; 1.4% of the twice-daily group discontinued due to photosensitivity. Jaundice led to discontinuation in <1% of the once-daily group versus 1.4% in the twice-daily group.[31]

Results from SILEN-C3 further streamlined duration of therapy for treatment-naive people with HCV genotype 1. Treatment with 12 or 24 weeks of once-daily 120 mg BI 201335 and PEG-IFN/RBV (followed by response-guided PEG-IFN/RBV for 24 weeks) was equally effective, with SVR of 65% versus 73%.[32]

Asunaprevir (BMS-650032)

Asunaprevir, a twice-daily protease inhibitor from BMS is being studied with the company's other DAAs (the NS5a inhibitor daclatasvir and BMS-791325, a non-nucleoside polymerase inhibitor), with or without pegylated interferon alfa or pegylated interferon lambda (see Meek as a Lambda, page 148) and ribavirin. Asunaprevir is active against HCV genotype 4. At higher doses, asunaprevir caused liver-enzyme elevations; the dose has been lowered from 600 mg twice daily to 200 mg twice daily.[21,33]

Asunaprevir's twice-daily dosing may limit its use. A recently announced agreement between BMS and Janssen to study daclatasvir with Janssen's protease inhibitor, simeprevir, may not bode well for asunaprevir.

GS-7977

Adding GS-7977 to PEG-IFN/RBV can shorten treatment and boost cure rates in non-cirrhotic treatment-naive people with HCV genotype 1, according to results from ATOMIC, a 332-person trial. ATOMIC compared 12 weeks of triple therapy to 24 weeks of triple therapy; a third arm looked at 12 weeks of triple therapy followed by GS-7977 plus ribavirin or GS-7977 monotherapy. Most of ATOMIC's participants had an IL28B CT or TT genotype, and HCV genotype 1a.

In all treatment arms, HCV RNA rapidly became undetectable and remained undetectable throughout treatment. At 12 weeks after treatment completion, 90% of the 12-week treatment group had undetectable HCV RNA. In people treated for 24 weeks, HCV RNA remained undetectable 4 weeks after treatment completion in 92%. No viral breakthrough occurred; there were four relapses. To date, no evidence of S282T, a mutation associated with nucleotide resistance, has been detected among relapsers; results from resistance testing using deep sequencing are pending.

Serious adverse events were reported in 10% (5/52) of the people in the 12-week treatment arm, and 8% (4/52) discontinued treatment; one discontinuation was attributed to GS-7977. In the 24-week treatment groups, 5% (4/125) had a serious adverse event, and 15% (12/125) discontinued treatment due to adverse events. Of these adverse events, 5% (6/125) were related to GS-7977. In the groups treated with 12 weeks of triple therapy followed by 12 weeks of GS-7977 plus ribavirin or GS-7977 monotherapy, 4% (3/156) experienced a serious adverse event, 4% (6/156) discontinued treatment, and <1% (1/156) had adverse events related to GS-7977.

The most common adverse events, reported in >15% of study participants, were fatigue, headache, nausea, insomnia, chills, rash, anemia, fever, appetite loss, diarrhea, and neutropenia. Laboratory abnormalities improved quickly after discontinuation of pegylated interferon.[34]

Daclatasvir (BMS-790052)

Bristol-Myers Squibb's first-in-class, once-daily, pan-genotypic NS5a inhibitor, daclatasvir, is in phase III. Daclatasvir is likely to be a therapeutic backbone, since it has been studied—and is effective—in interferon-free regimens with GS-7977 or asunaprevir (BMS-650032). Daclatasvir is also being studied with BMS-986094 (formerly INX-189), in triple therapy (with either pegylated interferon alfa or pegylated interferon lambda, plus ribavirin), and in quadruple therapy (with asunaprevir, pegylated interferon, and ribavirin).

Danoprevir/r

Hoffmann-La Roche and Genentech's danoprevir/r (RG7227) is a twice-daily, ritonavir-boosted HCV protease inhibitor with activity against HCV genotypes 1, 4 and 6. DAUPHINE, an ongoing phase II trial in 421 treatment-naive people with HCV genotypes 1 and 4, is comparing doses (200, 100, and 50 mg danoprevir, boosted with 100 mg ritonavir, twice-daily) and response-guided therapy with danoprevir/r plus PEG-IFN/RBV. At 12 weeks after treatment completion, HCV RNA was undetectable in 86% of the highest-dosing arm, 77% of the 100 mg arm, and 65% of the 50 mg arm.

Response to treatment in the 200 mg dosing arm did not differ according to HCV subtype or IL28B genotype; at 12 weeks after treatment completion, 88% of people with HCV subtype 1a and an IL28B non-CC genotype had undetectable HCV RNA. Across all dosing arms, HCV RNA remained undetectable 12 weeks after treatment completion in 100% of people with HCV genotype 4.

In the response-guided therapy arm, 76% of early responders (who were treated for 12 weeks) and 67% of late responders (treated for 24 weeks) maintained undetectable HCV RNA 12 weeks after treatment completion, bringing the overall total to 72%.

One death occurred during the trial—from sudden heart attack, in a participant with preexisting diabetes and hypertension—it was considered unrelated to study drugs. Adverse events were reported in virtually all study participants. Side effects from ritonavir, which is used to boost danoprevir levels, increased the likelihood of more than one serious adverse event among people in the danoprevir/r arms (range 4–9% vs. 1% for placebo). The rate of danoprevir/r-related treatment discontinuations was similar to the rate of PEG-IFN/RBV-associated discontinuations (3–7%, and 3–8%, respectively).

Common side effects (experienced by more than 15% of study participants) included fatigue, fever, chills, weakness, nausea, diarrhea, itching, rash, hair loss, headache, aching muscles and joints, insomnia, cough, and appetite loss. Diarrhea was the only side effect associated with danoprevir/r. Adding danoprevir/r did not increase rates of rash or anemia (known side effects of other HCV protease inhibitors). Most grade 3 and grade 4 lab abnormalities were neutropenia, reported in 22% to 38% of study participants.[35]

Meek as a Lambda?

A new, type III interferon, peginterferon lambda, may replace pegylated interferon alfa. Lambda interferon may have fewer side effects than alfa interferon, because there are fewer receptors for it outside of the liver.

EMERGE, an ongoing phase IIb trial in 526 treatment-naive, non-cirrhotic people with HCV genotypes 1, 2, 3, and 4, is comparing safety, tolerability, and efficacy of peginterferon lambda versus pegylated interferon alfa (in combination with ribavirin) for 24 to 48 weeks, depending on HCV genotype. Participants with genotypes 1 and 4 are still being followed in the study, but final results from 41 participants with genotype 2 and 3 are available. Participants were assigned to once-weekly injections of 120 μg, 180 μg, or 240 μg of peginterferon lambda, or 180 μg of pegylated interferon alfa plus daily ribavirin (the 180 microgram dose will be studied in phase III trials).

Cure rates were similar among people with HCV genotype 2 (70% of the 180 μg peginterferon lambda dosing arm vs. 66% for pegylated interferon alfa); in HCV genotype 3, 83% versus 40% were cured by lambda and alfa, respectively, although the number of participants (29 or 30 per study arm) makes it difficult to draw conclusions about efficacy.

There was no significant difference in serious adverse events between peginterferon lambda and pegylated interferon alfa, but fever, chills, and muscle and joint pain occurred less frequently with peginterferon lambda versus pegylated interferon alfa. Although the number of people in each dosing arm was small, there were marked differences in the rate of severe laboratory abnormalities. With peginterferon lambda, the incidence of neutropenia was 0% (vs. 27% with pegylated interferon alfa); anemia occurred in 7% (vs. 45%); and thrombocytopenia incidence was 0% (vs. 24%).

Unfortunately, the dreaded psychiatric side effects of interferon—depression, irritability, and insomnia—were more common with peginterferon lambda than with pegylated interferon alfa (≥40% vs. 33%), regardless of the dose.[36]

HCV Quadruple Therapy ("Quad")

As HCV drug development advances, optimizing treatment for people who are unlikely to respond—even if it means keeping interferon on board—should be prioritized (particularly since DAA regimens seem to cure people who are the easiest to treat successfully).

Experts have long recognized the immune system's critical role in successful HCV treatment. It is paradoxical that some people with poor interferon sensitivity (demonstrated by null response) are more likely to be cured by quad therapy (two DAAs from different classes plus PEG-IFN/RBV) than by interferon-free regimens. Yet quad therapy has demonstrated efficacy in null responders as well as in treatment-naive people.[23,33,37,38]

So far, people with HCV genotype 1a, especially null responders to interferon-based treatment, seem to have the most to gain from quad. Over 90% of null responders in a clinical trial—most with HCV genotype 1a, and all with IL28B CT or TT genotypes—maintained undetectable HCV RNA throughout treatment with quad, and for four weeks afterward.[23] Identifying those most likely to benefit from quad is challenging in the era of all-DAA trials, and likely to make enrollment and retention difficult unless pegylated interferon is used only as rescue therapy.

WELCOME TO AN INTERFERON-FREE WORLD

The year 2012 has ushered in the era of interferon-free therapy. Most trials have been in people who are treatment-naive, without cirrhosis. It is time for DAA trials to move into populations with the greatest need, informed by earlier trials in easier-to-treat populations.

Some of the factors associated with response to interferon-based treatment still apply when interferon is removed, and others have been identified. Determinants of successful treatment with DAAs include:

- Treatment-naive versus treatment-experienced;
- HCV subtype 1b versus 1a;
- IL28B genotype CC versus CT or TT genotype (although this can sometimes be overcome with a higher dose);
- Pretreatment IP-10 (interferon gamma–inducible protein 10) level: low versus high;
- Drug potency and resistance barrier;
- Drug concentration;
- Liver histology: mild-to-moderate liver damage versus cirrhosis;
- Baseline resistance;
- Appropriate treatment duration, according to regimen and population;
- Aggressive side effects management;
- Adherence to treatment; and
- Drug tolerability and safety: DAAs are described in press releases and at conferences as being "generally well tolerated," despite a range of adverse events and laboratory abnormalities that can be debilitating, or even life-threatening.

Getting to the Best: Clinical Collaborations

Without a public-private research partnership, opportunities for best-in-class treatment regimens are lost.

DAAs can be combined into regimens when drugs targeting different steps in the HCV life cycle are at a similar stage of development. Sometimes, a company is not able to combine its own drugs into regimens. Clinical collaboration among companies—an approach used in HIV—facilitates development of DAA regimens, benefiting study volunteers and, ultimately, patients as well as the companies who sell these drugs.

Pharmasset and Bristol-Myers Squibb (BMS) launched a clinical collaboration in January 2011, combining PSI-7977 (a nucleotide polymerase inhibitor) and the NS5a inhibitor daclatasvir into a once-daily, interferon-free regimen active against genotypes 1, 2, and 3. In July 2011, Pharmasset entered a clinical collaboration with Tibotec (now Janssen), creating another once-daily, interferon-free regimen with PSI-7977 and simeprevir (TMC435; an HCV protease inhibitor). In December 2011, BMS and Janssen announced plans to launch a phase II trial in mid-2012 combining daclatasvir with simeprevir. In April, the companies declared their intention to continue collaboration by advancing the combination into phase III, and to study drug-drug interactions between simeprevir and BMS-986094 (formerly known as INX-189; a nucleotide polymerase inhibitor). These collaborations are examples of best practices in drug development.

In 2012, Gilead Sciences purchased Pharmasset for US$11 billion dollars. Although Gilead is supporting ongoing clinical trials with BMS and Janssen, its future participation in clinical collaborations is uncertain. Gilead has six other DAAs from four different classes in clinical development: two non-nucleoside polymerase inhibitors, two protease inhibitors, a nucleoside polymerase inhibitor, and an NS5a inhibitor (which it quickly advanced into a trial with GS-7977).

Gilead may decide not to collaborate with anyone—regardless of the benefit to patients—in order to gain control of the market. Failure to collaborate will force patients to wait for an in-house combination, provided all goes well with the development of BMS's nucleotide and Gilead's NS5a inhibitor. Unfortunately, both of these drugs are in an earlier stage of development than are daclatasvir and GS-7977.

Waiting for the Cure

Reporting posttreatment results as early as possible has become customary at scientific meetings. But the wait to determine a cure may take longer than 24 weeks. Without interferon, SVR-24 is called into question.

When Is a Cure Really a Cure?

Early response rates may ultimately become predictive of cure rates, but more data are needed to confirm their validity. At present, their predictive value is unclear, since relapse occurs at different time points, depending on drug, regimen, and patient-specific characteristics. For example, in ELECTRON, after 12 weeks of GS-7977 and ribavirin, 9 of 10 null responders with HCV genotype 1 relapsed within 4 weeks; a later relapse, at 8 weeks posttreatment, was reported in 1 of 15 people in another arm of ELECTRON (treatment-experienced people with HCV genotypes 2 and 3).[39,40] A single late relapse—at posttreatment week 36—occurred in a treatment-naive study participant treated with ribavirin plus two experimental drugs from Abbott Laboratories, a boosted protease inhibitor (ABT-450/r) and a non-nucleoside polymerase inhibitor (ABT-072).[41]

SVR-4 (sustained virological response at 4 weeks after treatment completion): HCV RNA becomes undetectable during treatment and remains undetectable 4 weeks afterward. SVR-4 is not validated as a predictor of treatment outcome, since relapse may take longer than 4 weeks to occur.

SVR-12 (sustained virological response at 12 weeks after treatment completion): HCV RNA becomes undetectable during treatment and remains undetectable 12 weeks afterward. The U.S. Food and Drug Administration (FDA) accepted SVR-12 as an endpoint. SVR-12 is tightly correlated with SVR-24 in interferon-based regimens, since relapse almost always occurs within 12 weeks of treatment completion.

SVR-24 (sustained virological response at 24 weeks after treatment completion): HCV RNA becomes undetectable during treatment and remains undetectable for 24 weeks afterward. SVR-24 after interferon-based treatment is considered to be a cure, is durable (the late relapse rate is $<1\%$), and is known to decrease the incidence of liver-related illness and death.[42–45]

DAA COMBINATIONS: IN THE TREATMENT-NAIVE

Daclatasvir (BMS-790052) and GS-7977, with and without Ribavirin (HCV Genotypes 1, 2, and 3)

The exciting—but possibly short-lived—clinical collaboration between BMS and Gilead identified a winning combination of once-daily DAAs for 88 non-cirrhotic people with HCV genotypes 1, 2, and 3. A month after completing 24 weeks of treatment with GS-7977 and daclatasvir (with or without ribavirin), the SVR-4 rate was 100% in people with HCV genotype 1, and >85% in those with HCV genotypes 2 and 3, regardless of ribavirin use.[46] The trial is now looking at 12 weeks of treatment with the same drugs.

GS-7977 and Ribavirin (HCV Genotype 1)

In ELECTRON, 25 non-cirrhotic people with HCV genotype 1 were treated with GS-7977 and ribavirin for 12 weeks. Four weeks after treatment completion, HCV RNA remained undetectable in 22 of 25 study participants, yielding an SVR-4 rate of 88%.[40] Additional trials of shorter regimens are under way.

There were no discontinuations; adverse events were mild to moderate: four people each experienced a single adverse event: headache, nerve pain, chest pain, and vomiting; one experienced a drop in white blood cells.[39]

However, the same regimen was less effective for people with genotype 1 in QUANTUM, which is comparing 12 versus 24 weeks of treatment. In the 12-week treatment group, only 10 of 17 people had undetectable HCV RNA four weeks after finishing treatment, translating to an SVR-4 rate of 59%. QUANTUM participants differed from ELECTRON's; only 16% (3/19) had the IL28B CC genotype, versus 44% (11/25) of ELECTRON's participants. In QUANTUM, all of the relapses occurred in people with the IL28B CT or TT genotype. QUANTUM included people with cirrhosis—who have lower exposure to GS-7977 than people without cirrhosis—whereas ELECTRON did not.[47,48]

GS-7977 plus Ribavirin (with or without Pegylated Interferon); GS-7977 Monotherapy (HCV Genotypes 2 and 3)

GS-7977 has been studied in non-cirrhotic people with HCV genotypes 2 and 3. In the ELECTRON trial, 10 people were treated for 8 weeks, and 40 people were treated for 12 weeks, with GS-7977 and ribavirin with 0, 4, 8, or 12 weeks of pegylated interferon; 100% of them achieved SVR-24. A 12-week GS-7977 monotherapy arm was added; 60%, or 6 of 10 people, achieved SVR-24.

Adverse events were fewer in the interferon-free arm; 40% of participants reported experiencing one adverse event (vs. 50–72% in the interferon arms)—these were headache, fatigue, and aching muscles. No grade 3 or grade 4 laboratory abnormalities occurred among participants in the interferon-free arm, whereas one case of grade 3 anemia, three cases of grade 3 lymphopenia, thirteen cases of grade 3 neutropenia, nine cases of leukopenia, and four cases of grade 4 neutropenia were reported among participants who received interferon.[39]

ABT-450/r and ABT-072 plus Ribavirin (HCV Genotype 1)

Abbott's PILOT trial enrolled 11 non-cirrhotic people with HCV genotype 1 and an IL28B CC genotype, who were treated with 12 weeks of ABT-450/r (a ritonavir-boosted HCV protease inhibitor), ABT-072 (a non-nucleoside polymerase inhibitor), and ribavirin. One relapse occurred at 8 weeks after treatment completion. Although 91% achieved SVR-24, a late relapse at 36 weeks posttreatment lowered SVR to 82%. Both unsuccessfully treated people had HCV genotype 1a; although neither had evidence of resistance at baseline, protease resistance was found after the early relapse, and polymerase resistance after the late relapse.[41]

ABT-450/r and ABT-333 plus Ribavirin (HCV Genotype 1)

Abbott's COPILOT trial included non-cirrhotic treatment-naive, interferon-ineligible, or treatment-experienced, interferon-intolerant participants with HCV genotype 1. The SVR-12 rate among COPILOT's treatment-naive participants ranged from 93% to 95% after 12 weeks of triple therapy with ABT-450/r (a ritonavir-boosted protease inhibitor) once daily, ABT-333 (non-nucleoside polymerase inhibitor) twice daily, and ribavirin.

Serious adverse events included elevated bilirubin (managed with ribavirin dose reduction), fatigue, pain, and vomiting; none led to treatment discontinuation. One participant discontinued treatment after two weeks due to grade 3 liver-enzyme elevations, which resolved after treatment discontinuation.

COPILOT's most common side effects, experienced by >20% of study participants, were: fatigue, nausea, headache, dizziness, insomnia, rash, itching, and vomiting. Laboratory abnormalities (which included six cases of elevated bilirubin, attributed to ABT-450/r, and two cases of elevated creatinine) resolved during treatment.[49]

BI 201335 and BI 207127 plus Ribavirin (HCV Genotype 1)

Boehringer Ingelheim's five-arm SOUND-C2 trial identified a DAA regimen that is effective for treatment-naive people with HCV genotype 1b, and people with HCV genotype 1a who have the IL28B CC genotype. SOUND-C2, a 368-person trial, compared 16 to 40 weeks of treatment with BI 201335, a once-daily HCV protease inhibitor, and twice- versus thrice-daily BI 207127, a non-nucleoside polymerase inhibitor, with or without ribavirin. SVR-12 ranged from 39% in the no-ribavirin arm to 68% in people treated with 28 weeks of BI 201335 and twice-daily BI 207127 plus ribavirin.

Researchers found significant differences in SVR rates, according to HCV subtype (genotype 1a versus 1b) and IL28B genotype (CC versus non-CC). In the 68% SVR-12 treatment arm, SVR-12 was 43% in genotype 1a versus 83% for genotype 1b, and 64% for non-CC genotype versus 79% for CC genotype. Overall, SVR-12 among people with HCV genotype 1a, non-CC, was 32% versus 75% (1a, CC); in HCV genotype 1b, SVR-12 was 82% in non-CC, and 84% in CC.[50]

Tolerability of twice-daily BI 207127 was better than that of thrice-daily dosing, with no severe adverse events reported in the 28-week arm. Moderate adverse events led to nine discontinuations (jaundice [N = 2], vomiting [N = 3], and diarrhea [N = 4]) in the 28-week treatment arm. Laboratory abnormalities in the 28-week arm are as follows: elevated bilirubin (a previously reported side effect of BI 201335, attributed to blocked drug transporters): 26% grade 3, and 10% grade 4; ALT elevations: 3% grade 3; and anemia: 2% (one case each of grade 3 and grade 4).[50,51]

SOUND-C2 offers the first glimpse of DAA safety and efficacy in people with compensated cirrhosis. A group of 37 SOUND-C2 participants (or 10%) had cirrhosis; more than half (N = 25) had HCV genotype 1b. Overall, the SVR-12 with thrice-daily BI 207127 was 57%, versus 54% for twice-daily BI 207127 (and 33% for the no-ribavirin arm). As expected, SVR-12 was higher in HCV genotype 1b than HCV genotype 1a in all treatment arms; in the 28-week, twice-daily dosing arm, it was 71% (vs. 33%). Although viral breakthrough rates were higher in the twice-daily dosing arm than the thrice-daily dosing arm (38% vs. 19%), relapse rates were lower (0% vs. 8%).

In participants with cirrhosis, tolerability of twice-daily BI 207127 was superior to thrice-daily dosing. All participants in the twice-daily arm experienced adverse events; serious adverse events were reported in 15% (N = 2) of participants in the twice-daily group, with one case of anemia leading to

treatment discontinuation. In the thrice-daily arm, 19% experienced serious adverse events that caused six people to discontinue treatment; these were rash, photosensitivity, and jaundice. Elevations in bilirubin—without liver dysfunction—were attributed to BI 201335.[52]

Additional trials are planned in people with HCV genotype 1b and HCV genotype 1a—CC only—due to high rates of viral breakthrough and relapse in people with HCV genotype 1a and non-CC genotypes.[50]

Danoprevir/r and Mericitabine, plus Ribavirin (HCV Genotypes 1 and 4)

Roche's phase IIb study, INFORM-SVR, is combining response-guided therapy with danoprevir/r, a twice-daily ritonavir-boosted HCV protease inhibitor, and mericitabine, a twice-daily nucleoside polymerase inhibitor, with or without ribavirin for 12 to 24 weeks in non-cirrhotic people with HCV genotype 1. The original study design was modified after high relapse rates were observed in the 12-week treatment and ribavirin-free arms. Treatment was extended to 24 weeks, and ribavirin was given to all participants.

The majority of INFORM-SVR participants were male, had HCV genotype 1a, and non-CC genotypes. Of the 64 people treated for 24 weeks with all three drugs, 41% experienced SVR-12. People with HCV genotype 1b were more likely to achieve SVR-12 (71% versus 26% in HCV genotype 1a). In contrast, SVR-12 was more likely among people with non-CC genotypes (32% for CC versus 44% for non-CC), although only 4 people had HCV genotype 1b and CC genotype. Breakthrough rates were higher in people who did not receive ribavirin, and in HCV genotype 1a versus 1b. Resistance to danoprevir/r was observed in all patients who experienced viral breakthrough; mericitabine resistance was found in one person.

Almost all participants had more than one adverse event; a total of 567 mild-to-moderate events were reported among 83 people. The most common side effects, occurring in >10% of people were headache, fatigue, nausea, diarrhea, colds, insomnia, itching, weakness, dizziness, irritability, shortness of breath, cough, upset stomach, painful joints, and vomiting. As for laboratory abnormalities, one person experienced grade 3 anemia, four people had grade 3 lipid elevations, and one case each of grade 3 elevations in phosphate and lipase were observed.

A single serious adverse event, multiple myeloma, occurred 53 days after treatment completion and one person discontinued due to pain in the back of the throat (it was not specified whether or not this was a treatment-related adverse event).[53]

DAA COMBINATIONS IN THE TREATMENT-EXPERIENCED AND INTERFERON-INELIGIBLE/INTOLERANT

Results from interferon-free trials in treatment-experienced people and those ineligible for, or intolerant of, pegylated interferon have been mixed.

ABT-450/r and ABT-333 plus Ribavirin* (HCV Genotype 1)

Abbott's COPILOT trial included 17 non-cirrhotic partial- or null responders with HCV genotype 1, who were treated for 12 weeks with ABT-450/r (a once-daily, ritonavir-boosted HCV protease inhibitor), ABT-333 (a twice-daily HCV non-nucleoside polymerase inhibitor), and ribavirin—the same regimen given to COPILOT's treatment-naive participants.

In this treatment-experienced group, SVR-12 was 47% (vs. 93–95% among treatment-naive participants). During treatment, six viral breakthroughs—all but one in people with HCV genotype 1a—occurred in people with no pretreatment resistance; after breakthrough, resistance to both protease- and polymerase inhibitors was found in all of them. In the lone genotype 1b breakthrough, resistance to HCV protease inhibitors was found at baseline; resistance to both classes was detected after treatment. Relapse occurred in three participants, all with HCV genotype 1a; none had pretreatment resistance, but two of three had resistance to both drug classes after relapse.[49]

* COPILOT's adverse events are described on page 153, since it included treatment-naive participants.

Daclatasvir and Asunaprevir (HCV Genotype 1)

BMS has a highly effective in-house combination for non-cirrhotic null responders with HCV genotype 1b. After 24 weeks of treatment with dual DAAs (once-daily daclatasvir, and asunaprevir, a twice-daily protease inhibitor), SVR-24 was 77% among a group of 21 null responders and 23 interferon-ineligible/intolerant participants. This phase IIa, open-label trial was conducted in Japan, where HCV genotype 1b is highly prevalent. SVR-24 was higher among null responders (91%) than among interferon-ineligible/intolerant participants (64%).

Although ten study participants had pretreatment resistance to daclatasvir, five of them achieved SVR-24. There were three viral breakthroughs, and four people relapsed; most had lower drug concentrations than people who achieved SVR-24. Researchers speculated that the combination of preexisting

drug resistance and lower drug exposure could have led to treatment failure, since people with either one of these were successfully treated.

During treatment, five study participants experienced serious adverse events (high fever, gastroenteritis, and elevated bilirubin—which were unrelated to study drugs—and hypochondria). There were three discontinuations; two for liver-enzyme elevations and one for elevated bilirubin. The adverse events experienced by at least three participants included headache, cold, diarrhea, fever, stomach pain, malaise, constipation, back pain, and appetite loss. Grade 3 and 4 laboratory abnormalities included abnormal elevations in white blood cells, liver enzymes (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), bilirubin, and phosphorous.[21,22]

GS-7977 and Ribavirin (HCV Genotypes 1, 2, and 3)

GS-7977 is less effective for people who are treatment-experienced, regardless of HCV genotype. In the ELECTRON study, 9 of 10 non-cirrhotic null responders with HCV genotype 1 relapsed within four weeks of completing 12 weeks of treatment with GS-7977 and ribavirin. In this group, HCV RNA became undetectable within four weeks and remained undetectable throughout, suggesting that extending treatment and/or adding anther DAA may do the trick. The only cure occurred in a participant with characteristics associated with successful HCV treatment: she was a young Caucasian woman with the IL28B CC genotype and barely any fibrosis.

Among null responders, one person experienced anxiety, depression, and a sprained ankle; there was one case of anemia; and one case of low platelets (in a participant using warfarin, a blood thinner) was reported.[39]

The same regimen, 12 weeks of GS-7977 and ribavirin, has been studied in a group of treatment-experienced people with HCV genotypes 2 and 3 (defined as relapsers, partial responders, and null responders). There was SVR-4 in 80% (12 of 15) of the participants. An additional relapse was reported at 8 weeks after treatment completion. Adverse events were mild to moderate, with two cases of headache, and no laboratory abnormalities.[40]

DAAS IN HIV/HCV-COINFECTED PEOPLE

Rapid HCV Progression vs. Slow Drug Development

Hepatitis C remains a common—and dangerous—coinfection among HIV-positive people. Worldwide, an estimated 5 million people are HIV/HCV-coinfected.[54] The benefits of antiretroviral therapy have been offset by an increased risk of death associated with hepatitis C among HIV/HCV-coinfected people.[55] In fact, end-stage liver disease secondary to hepatitis C is a leading cause of death among people with HIV/AIDS where antiretroviral therapy (ART) is widely available.[56–60]

Treating—and curing—hepatitis C in coinfected people significantly reduces the rate of progression to AIDS, death from AIDS and non-AIDS-related causes, as well as liver-related illness and death.[61,62] It is time to move interferon-free trials into HIV/HCV-coinfected people. As of mid-2012, there are no clinical trials of dual- or multiple DAAs or quad in HIV-positive people.

Trials of response-guided therapy and trials in coinfected people who are HCV treatment-experienced are planned or ongoing (see Table 2. HCV Treatment Trials in HIV/HCV-Coinfected People).

HCV Protease Inhibitors in HIV/HCV-Coinfected People

The first trials of HCV protease inhibitor–based therapy in HIV/HCV-coinfected people opened in 2009, prior to issuance of the FDA's draft guidance for industry *Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment*, which stipulated that single-arm prospective trials with historical controls could be used for HIV/HCV-coinfected patients "if trials in the HCV monoinfected population showed robust and substantial efficacy of the new DAA added to SOC [standard of care]."[63] Thus, both of these trials had a placebo arm, which may have slowed enrollment.

Adding boceprevir or telaprevir to PEG-IFN/RBV boosts cure rates among coinfected people. Two small, 48-week phase II trials found that both the safety profile and response to treatment with an HCV protease inhibitor plus PEG-IFN/RBV were similar, regardless of HIV status.[10,11,64,65]

The overall SVR-12 rate was 74% with telaprevir-based treatment (vs. 45% in the PEG-IFN/RBV control group). Participants began treatment with 12 weeks of triple therapy, followed by a 36-week "tail" of PEG-IFN/RBV.

Treatment was discontinued by 42% (16/38) of the participants in the telaprevir arm: 5% (2/38) for treatment failure; 8% (3/38) due to adverse events; and 32% (11/38) for various reasons, including noncompliance, lost to follow-up, and withdrawal of consent. In the control arm, 32% (7/22) stopped due to treatment failure, and 9% (2/22) discontinued due to relocation or because they did not want to remain in the trial.[64]

With boceprevir-based treatment, SVR-12 was 60% (versus 26% in the PEG-IFN/RBV control group). Participants began treatment with a four-week PEG-IFN/RBV lead-in, followed by 44 weeks of triple therapy.

Treatment was discontinued by 38% (24/64) of those in the boceprevir arm: 20% (13/64) due to adverse events; 9% (6/64) due to treatment failure; and the remainder (5/64) lost to follow-up, non-compliant, or did not want to continue participating in the trial. In the control arm, 53% (18/34) discontinued treatment: 9% (3/34) for adverse events, 41% (14/34) for treatment failure, and 3% (1/34) for reasons unrelated to treatment. Unfortunately, boceprevir and telaprevir add side effects to a regimen that is already poorly tolerated (see Table 3. Adverse Events among HIV/HCV-Coinfected Study Participants).

TABLE 2. HCV Treatment Trials for HIV/HCV-Coinfected People

Drug/Class/Sponsor	Study Population	Strategy	Status
boceprevir (protease inhibitor) National Institute of Allergy and Infectious Diseases	HCV or HIV/HCV genotype 1, treatment-naive	4-week PEG-IFN/RBV "lead-in" followed by response-guided triple therapy	Phase IV; N=200 Open for enrollment
BI 201335 (protease inhibitor) Boehringer Ingelheim	HIV/HCV genotype 1, treatment-naive or relapser	Response-guided triple therapy	Phase III; N=316 Open for enrollment
BMS-790052 (daclatasvir) (NS5a inhibitor) Bristol-Myers Squibb	HIV/HCV genotype 1, treatment-naive	24 weeks of triple therapy followed by 24-week PEG-IFN/RBV "tail"	Phase III; N=300 Open for enrollment
boceprevir (protease inhibitor) National Institute of Allergy and Infectious Diseases	HIV/HCV genotype 1, treatment-naive, or treatment-experienced	4-week PEG-IFN/RBV "lead-in" followed by response-guided triple therapy	Phase III; N=310 Open for enrollment
simeprevir (TMC435) (protease inhibitor) Janssen R&D Ireland	HIV/HCV genotype 1, treatment-naive and treatment-experienced	Response-guided triple therapy	Phase III; N=107 Ongoing; no longer enrolling
telaprevir (protease inhibitor) Janssen-Cilag International NV	HIV/HCV genotype 1, with severe fibrosis or compensated cirrhosis who are ineligible for ongoing clinical studies of telaprevir	12 weeks of triple therapy followed by a 36-week PEG-IFN/RBV "tail"	Phase III; N=500 Open for enrollment
telaprevir (protease inhibitor) Vertex Pharmaceuticals	HIV/HCV genotype 1, treatment-naive and treatment-experienced	Response-guided triple therapy	Phase III; N=160 Open for enrollment
telaprevir (protease inhibitor) Tibotec	HIV/HCV genotype 1, treatment-naive or treatment-experienced	Response-guided triple therapy	Phase IIIb; N=150 Not open as of 5/25/12

TABLE 3. Adverse Events among HIV/HCV-Coinfected Study Participants

Adverse Event (AE)	Boceprevir + PEG-IFN/RBV Reported as: most common events with a difference of ≥10% between boceprevir versus PEG-IFN/RBV control	Telaprevir + PEG-IFN/RBV Reported as: most common events in >15% of patients, regardless of severity
Any AE	98%	100%
Serious AE	8%	20%
Discontinuation due to AE	14%	5%
Fatigue	Not reported	42%
Puritis	Not reported	39%
Headache	28%	37%
Nausea	Not reported	34%
Rash	Not reported	34%
Diarrhea	Not reported	24%
Dizziness	Not reported	21%
Pyrexia	34%	21%
Depression	Not reported	21%
Neutropenia	13%	21%
Anemia	30%	18%
Vomiting	25%	18%
Myalgia	Not reported	16%
Chills	Not reported	16%
Insomnia	Not reported	13%
Decreased Appetite	30% vs. 18%	11%
Weight loss	Not reported	11%
Dysgeusia	25%	Not reported

Sources:
Sherman KE, Rockstroh JK, Dieterich DT, et al. Telaprevir combination with peginterferon alfa-2a/ribavirin in HCV/HIV coinfected patients: 24-week treatment interim analysis (Abstract LB-8). Paper presented at: 62nd Annual Meeting of the American Association for the Study of Liver Disease; 2011 November 4–8; San Francisco, CA.

Sulkowski M, Pol S, Cooper C, et al. Boceprevir plus peginterferon/ribavirin for the treatment of HCV/HIV co-infected patients: interim on-treatment results (Abstract LB-37). Paper presented at: 49th Annual Meeting of the Infectious Diseases Society of America (IDSA 2011); 2011 October 20–23; Boston, MA.

TABLE 4. Drug-Drug Interactions between HCV DAAs and HIV Antiretroviral Agents

Antiretroviral Drug and Class	Boceprevir (HCV Protease Inhibitor)	Telaprevir (HCV Protease Inhibitor)
atazanavir/r (ritonavir-boosted HIV protease inhibitor)	Boceprevir decreases atazanavir/r, although atazanavir/r does not have a significant effect on boceprevir **Coadministration not recommended**	Telaprevir increases atazanavir/r; atazanavir/r reduces telaprevir **Can coadminister without dose adjustment**
darunavir/r (ritonavir-boosted HIV protease inhibitor)	Boceprevir decreases darunavir/r; in turn, darunavir/r decreases boceprevir **Coadministration not recommended**	Telaprevir decreases darunavir/r; darunavir/r decreases telaprevir **Coadministration not recommended**
dolutegravir (HIV integrase inhibitor currently in phase III)	Drug-drug interaction study under way	Drug-drug interaction study under way
efavirenz (HIV non-nucleoside reverse transcriptase inhibitor)	Efavirenz reduces boceprevir **Coadministration not recommended**	Reduces telaprevir levels **Can be coadministered with telaprevir dose adjustment** (increase from 750 mg/TID to 1,125 mg/ TID)
etravirine (HIV non-nucleoside reverse transcriptase inhibitor)	Etravirine has an inconsistent effect on boceprevir; boceprevir reduces etravirine; clinical significance unclear	No data available
fosamprenavir/r (ritonavir-boosted HIV protease inhibitor)	No data available **Coadministration with ritonavir-boosted protease inhibitors is not recommended**	Telaprevir decreases fosamprenavir/r; fosamprenavir/r decreases telaprevir **Coadministration not recommended**
lopinavir/r (Ritonavir-boosted HIV protease inhibitor)	Boceprevir decreases lopinavir/r; in turn, lopinavir/r decreases boceprevir **Coadministration not recommended**	Telaprevir does not change lopinavir/r; lopinavir/r decreases telaprevir **Coadministration not recommended**
raltegravir (HIV integrase inhibitor)	**Can coadminister without dose adjustment**	Telaprevir increases raltegravir; raltegravir does not affect telaprevir **Can coadminister without dose adjustment**
ripilvirine (HIV non-nucleoside reverse transcriptase inhibitor)	No data available	No data available
ritonavir (HIV protease inhibitor used at lower doses as a pharmacokinetic booster)	Boceprevir decreases ritonavir **Coadministration not recommended**	No data available
tenofovir (HIV nucleotide reverse transcriptase inhibitor)	Boceprevir increases tenofovir by approximately 30%; tenofovir does not affect boceprevir **Can coadminister with monitoring for side effects/toxicity**	Telaprevir increases tenofovir by approximately 30%; tenofovir does not affect telaprevir **Can coadminister with monitoring for side effects/toxicity**

	Simeprevir (TMC435) (HCV Protease Inhibitor)	Daclatasvir (BMS-790052) (NS5a Inhibitor)
	No data available	**Can coadminister with daclatasvir dose adjustment** (to 30 mg)
	No data available	No data available
	No data available	No data available
	Efavirenz reduces simeprevir **Coadministration not recommended**	**Can coadminister with daclatasvir dose adjustment** (90 mg)
	No data available	No data available
	No data available	No data available
	No data available	No data available
	Can coadminister without dose adjustment	No data available
	Can coadminister without dose adjustment	No data available
	No data available	No data available
	Can coadminister without dose adjustment	**Can coadminister without dose adjustment**

Sources:

Bifano M, Hwang C, Oosterhuis B, et al. Assessment of HIV ARV drug interactions with the HCV NS5A replication complex inhibitor BMS-790052 demonstrates a pharmacokinetic profile which supports co-administration with tenofovir disoproxil fumarate, efavirenz, and atazanavir/ritonavir (Abstract 618). Paper presented at: 19th Conference on Retroviruses and Opportunistic Infections; 2012 March 5–8; Seattle, WA.

de Kanter C, Blonk M, Colbers A, et al. The influence of the HCV protease inhibitor boceprevir on the pharmacokinetics of the HIV integrase inhibitor raltegravir (Abstract 772 LB). Paper presented at: 19th Conference on Retroviruses and Opportunistic Infections; 2012 March 5–8; Seattle, WA.

Hammond K, Wolfe P, Burton J, et al. Pharmacokinetic interaction between boceprevir and etravirine in HIV/HCV seronegative volunteers (Abstract O_15). Paper presented at: 13th International Workshop on Clinical Pharmacology of HIV Therapy; 2012 April 16–18; Barcelona, Spain.

Hulskotte E, Feng H-P, Xuan F, et al. Pharmacokinetic interaction between the HCV protease inhibitor boceprevir and ritonavir-boosted HIV-1 protease inhibitors atazanavir, lopinavir, and darunavir (Abstract 771 LB). Paper presented at: 19th Conference on Retroviruses and Opportunistic Infections; 2012 March 5–8, 2012; Seattle, WA.

Kasserra C, Hughes E, Treitel M, et al. Clinical pharmacology of boceprevir: metabolism, excretion, and drug-drug interactions (Abstract 118). Paper presented at: 18th Conference on Retroviruses and Opportunistic Infections. 2011 February 27–March 2; Boston, MA.

Ouwerkerk-Mahadevan S, Sekar V, Peeters M, et al. The pharmacokinetic interaction of the HCV protease inhibitor TMC 435 with RPV, TDF, EFV or RAL in healthy volunteers (Abstract 49). Paper presented at: 19th Conference on Retroviruses and Opportunistic Infections; 2012 March 5–8; Seattle, WA.

Van Heeswijk R, Vandevoorde A, Boogaerts G, et al. Pharmacokinetic interactions between ARV agents and the investigational HCV protease inhibitor telaprevir in healthy volunteers (Abstract 119). Paper presented at: 18th Conference on Retroviruses and Opportunistic Infections; 2011 February 27–March 2; Boston, MA.

UP AND COMERS

Nucleoside and Nucleotide Polymerase Inhibitors

In January 2012, BMS purchased Inhibitex for approximately US$2.5 billion dollars, largely to get hold of INX-189 (now known as BMS-986094), a nucleotide in phase II. Data were expected in mid-May; hopefully, rumors about preclinical toxicity will not be substantiated.

Vertex has licensed two nucleotides from Alios Biopharma, ALS-2200 and ALS-2158, at a bargain price: US$60 million up front with a future payment of US$1.5 billion. They are currently in phase I, moving from healthy volunteers into a seven-day study in people with HCV. Data are expected in mid-2012.

Gilead's GS-6620 is not expected to move out of phase I unless drug delivery can be optimized. Idenix has a preclinical nucleotide candidate, IDX19368.

NS5a Inhibitors

Achillion has two once-daily, pan-genotypic candidates in phase I. ACH-2928 has been studied in healthy volunteers and people with HCV. ACH-3102 may be active against resistant HCV; it is now being studied in healthy volunteers.

EDP-239, from Enanta and Novartis, is entering phase I; it is a once-daily drug and is active against multiple genotypes. Merck's MK-8742 has entered a phase I trial in the Republic of Moldova; it may be active against resistant HCV and demonstrates activity against multiple genotypes, but may be less active against HCV genotype 2b. PPI-668 from Presidio Pharmaceuticals is a once-daily pan-genotypic NS5a inhibitor in phase Ia/Ib. Medivir has an unnumbered candidate in preclinical development.

Protease Inhibitors

Achillion's pan-genotypic ACH-2684 is in phase I.

Non-Nucleoside Polymerase Inhibitors

Gilead's GS-9669 is in phase I. Presidio's PPI-338 is in preclinical development; it offers once-daily dosing and may be unlikely to interact with many commonly used drugs. TMC647, from Janssen and Medivir, is in preclinical development. In contrast, Pfizer's filibuvir has not budged from a completed phase II trial launched in 2009.

Innovation without Access

Pharmaceutical companies and investment advisors have been avidly spinning results from small clinical trials of carefully selected participants into billions of dollars. Goldman Sachs predicted that the first DAAs would boost spending on HCV treatment in the next few years from US$3 billion to US$10 billion annually; other pundits forecast that the market for HCV drugs will swell to US$16 billion by 2015.

The hyperbole about new DAAs exists in sharp contrast to the lack of resources, infrastructure, and implementers needed to roll out programs to educate, test, diagnose, and treat millions of people. All over the world, people with HCV are hoping to gain access to a cure. Profit is leading a stampede over the basic human right to treatment for a potentially fatal—but curable—infection.

It does not matter how good the drugs are if people are undiagnosed, or cannot gain access to them. High drug prices will keep a cure out of reach for most of the 160 million people with hepatitis C.[6] Although drug pricing varies by country, the cost of HCV protease inhibitors is prohibitive in low- and middle-income countries, and limits access in wealthier countries. In the United States, where almost 50 million people currently have no medical coverage, the cost of an HCV protease inhibitor ranges from approximately US$32,000 to over US$52,000.[66]

Even without an HCV protease inhibitor, treatment with pegylated interferon and ribavirin is too expensive for people in most countries. Although ribavirin is available as a generic, and can be produced cheaply, Pegasys remains under patent by Hoffmann-La Roche in the United States, Europe, and Japan until 2017, and Merck's PEG-Intron is under patent in the United States, Europe, and Japan until 2016, keeping prices high.

It is possible to provide pegylated interferon and ribavirin in resource-limited settings; a precedent has been set by activists and policy makers in Egypt and in Thailand, who have broadened access by negotiating lower prices for pegylated interferon (see Hepatitis C (HCV) Treatment Access: Spotlight on Thailand/Asia, page 185).

If the world is to benefit from therapeutic advances in HCV treatment, 2013 should become the year of implementation. It is time to prepare health care systems for the people who will enter them for testing, care, and treatment.

Nomenclature: The Terms, They Are a-Changing*

DAAs are a new therapeutic territory. Interferon-era terms, time frames, and endpoints may not be applicable to DAA trials. New terms to describe responses to interferon-free regimens will facilitate cross-drug and cross-regimen comparisons by providing consistency across studies. To this end, experts in the field have developed new nomenclature for DAA trials. They recommend specifying the assay's lower limit of quantification, reporting viral decline in increments of 0.1 $\log_{10}$, and using these figures:

- **W#** to indicate week of treatment
- **Q** for quantifiable HCV RNA
- **U** for unquantifiable HCV RNA
- **TD/TND** to indicate whether or not target HCV RNA was detected
- **LIW/D** for duration of treatment lead-in, by weeks or days

TABLE 5. Nomenclature in Action

Current Terminology	New Nomenclature
RVR (rapid virological response, HCV RNA is undetectable after 4 weeks of treatment)	**W#4U$_{TND}$**
cEVR (complete early virological response; HCV RNA is undetectable at week 4 and remains undetectable at week 12)	**W#12U$_{TND}$**
2 $\log_{10}$ decrease in HCV RNA at week 2	**W#2Q [-2]**
2 $\log_{10}$ decrease in HCV RNA at week 2 with a 4-week lead-in	**LI$_{4W}$W2Q [-2]**

Source: Jensen DM, Wedemeyer H, Godofsky E, et al.; On Behalf of the Definitions/Nomenclature Working Group of the HCV Drug Development Advisory Group. Consensus recommendations for virologic nomenclature in DAA trials (Abstract 897). Paper presented at: 47th Annual Meeting of the European Association for the Study of the Liver; 2012 April 18–22; Barcelona, Spain.

*Data are reported in this chapter as they were presented, to avoid confusion.

RESOURCES

ClinicalTrials.gov (www.clinicaltrials.gov) provides information on HCV clinical trials and research.

HCV Advocate (www.hcvadvocate.org) offers conference reporting and an up-to-date HCV pipeline chart; available at: www.hcvadvocate.org/hepatitis/hepC/HCVDrugs.html.

HIV and Hepatitis.com (www.hivandhepatitis.com) offers news and conference reports.

NATAP (National AIDS Treatment Advocacy Project) (www.natap.org) offers comprehensive coverage of HCV and HIV/HCV coinfection.

TABLE 6. Nucleoside/Nucleotide Polymerase Inhibitors in Phase II and III

Agent/Dose/Sponsor	Phase/Population/Duration	Comments
BMS-986094 (formerly INX-189) 25 mg, 50 mg, 100 mg, 200 mg Once-daily Bristol-Myers Squibb	Phase II Genotypes 2 and 3 Treatment-naive 12 weeks	Being studied + RBV + PEG-IFN/RBV + daclatasvir (BMS-790052, an NS5a inhibitor)
GS-7977 (formerly PSI-7977) 400 mg Once-daily Gilead Sciences	Phase II and phase III Genotypes 2 and 3 Treatment-naive (interferon-unwilling/ineligible) and treatment-experienced (interferon-intolerant) 12–16 weeks Genotypes 1, 2, 3, 4, 5, & 6 Treatment-naive and treatment-experienced (includes HCV protease inhibitor-experienced) 12–48 weeks	Being studied as monotherapy + RBV + PEG-IFN/RBV + simeprevir (TMC435, a protease inhibitor) + simeprevir and RBV + daclatasvir (BMS-790052, an NS5a inhibitor) + daclatasvir and RBV + GS-5885 (an NS5a inhibitor) + GS-5885 and RBV First DAA study in people with HCC (pretransplant), split dosing (200 mg twice daily)
IDX-184 50 mg, 100 mg Once-daily Idenix	Phase II Genotype 1 Treatment-naive 24 or 48 weeks	Being studied + PEG-IFN/RBV

Agent/Dose/Sponsor	Phase/Population/Duration	Comments
mericitabine (formerly RG7128) 500 mg, 1,000 mg, 1,500 mg Twice-daily Hoffmann-La Roche	Phase II Genotypes 1 and 4 Treatment-naive and treatment-experienced (null responders) 24–48 weeks Genotype 1b and 4 Treatment-naive or interferon-intolerant/ineligible 24 weeks Genotypes 1 and 4 Treatment-naive or treatment-experienced (null responders) with cirrhosis 24 weeks Genotype 1 Treatment-experienced (partial- or null responders) 24–48 weeks Genotype 1 Protease inhibitor-experienced (breakthrough, partial responders, and relapsers) 24–26 weeks	Being studied + PEG-IFN/RBV + danoprevir/r (ritonavir-boosted protease inhibitor) + danoprevir/r and RBV + danoprevir and PEG-IFN + danoprevir/r with PEG-IFN/RBV (in protease inhibitor-experienced) + telaprevir (protease inhibitor) with PEG-IFN/RBV (null responders) + boceprevir (protease inhibitor) with PEG-IFN/RBV (null responders) Protease inhibitor–experienced not open as of 6/12

TABLE 7. NS5a Inhibitors in Phase II and III

Agent/Dose/Sponsor	Phase/Population/Duration	Comments
ABT-267 5 mg, 50 mg, 200 mg Once-daily Abbott Laboratories	Phase II Genotypes 1, 2, and 3 Treatment-naive 12–48 weeks Genotype 1 Treatment-experienced (null responders) Up to 24 weeks	Being studied + PEG-IFN/RBV + ABT-450/r (ritonavir-boosted protease inhibitor) + ABT-450/r and RBV + ABT-333 (non-nucleoside polymerase inhibitor) + ABT-450/r and ABT-333 + ABT-450/r and ABT-333 with RBV (triple and quad therapy in treatment-naive and null responders)
daclatasvir (BMS-790052) 60 mg Once-daily Bristol-Myers Squibb	Phase II and Phase III Genotype 1 Treatment-naive 16–24 weeks Genotype 1 Treatment-naive African American/Latino and Latina/Caucasian 24–48 weeks Genotypes 1, 2, and 3 Treatment-naive 12 or 24 weeks Genotype 4 Treatment-naive 24–48 weeks Genotypes 1 and 4 Treatment-experienced (partial- and null responders) 24 weeks	Being studied + peginterferon lambda (BMS-914143) + peginterferon lambda and RBV + asunaprevir (BMS-650032, a protease inhibitor) + peginterferon lambda, with asunaprevir and RBV + PEG-IFN/RBV + GS-7977 (formerly PSI-7977, a nucleotide polymerase inhibitor) + GS-7977 and RBV + BMS-791325 (non-nucleoside polymerase inhibitor) + BMS-791325 and asunaprevir + asunaprevir with PEG-IFN/RBV + BMS-986094 (formerly INX-189, a nucleotide polymerase inhibitor) + BMS-986094 and RBV Null- and partial responder quad trials not open as of 6/12

Agent/Dose/Sponsor	Phase/Population/Duration	Comments
GS-5885 30 mg and 90 mg Once-daily Gilead Sciences	Phase II Genotype 1 Treatment-naive IL28B CC only 6–12 weeks Genotype 1 Treatment-naive 12–24 weeks Genotype 1 Treatment-naive Up to 48 weeks Genotype 1 Treatment-experienced (null responders) 12 weeks Genotype 1 Interferon-ineligible/ intolerant 24 weeks Genotype 1 Treatment-experienced (breakthrough, partial- and null responders, and relapsers) 24–48 weeks	Being studied + PEG-IFN/RBV + GS-9451 (a protease inhibitor) and RBV + GS-9451 and tegobuvir (GS-9190), a non-nucleoside polymerase inhibitor) + GS-9451 and tegobuvir with RBV + GS-9451 and tegobuvir, with PEG-IFN/RBV "rescue" + GS-9451 with PEG-IFN/RBV + GS-7977 (formerly PSI-7977, a nucleotide polymerase inhibitor) and RBV
GSK2336805 120 mg Once daily GlaxoSmithKline	Phase II Genotypes 1 and 4 Treatment-naive Up to 48 weeks	Being studied with PEG-IFN/RBV
IDX-719 1 mg – 100 mg Once-daily Idenix	Phase I and II Genotype 1 Treatment-naive Up to 13 days	Single and multiple doses assessed

TABLE 8. Protease Inhibitors in Phase II and III

Agent/Dose/Sponsor	Phase/Population/Duration	Comments
ABT-450/r 150 mg (boosted with 100 mg of ritonavir) Once-daily Abbott Laboratories	Phase II Genotype 1 Treatment-naive Duration not specified Genotype 1 Treatment-naive and treatment-experienced (non-responders) 12 weeks Genotypes 1, 2, and 3 Treatment-naive Duration not specified Genotype 1 Treatment-naive and treatment-experienced (null responders) Up to 24 weeks Genotype 1 Treatment-experienced (nonresponse to DAA regimen in Abbott trial) Up to 48 weeks	Being studied + ABT-333 (non-nucleoside polymerase inhibitor) + ABT-333 and RBV + ABT-267 (NS5a inhibitor) + ABT-267 and RBV + ABT-267 and ABT-333 + ABT-333 and ABT-267 with RBV + ABT-267 and PEG-IFN/RBV (quad for non-responders) Quad study not open as of 6/2012
ACH-1625 200 mg, 400 mg, 800 mg Once-daily Achillion Pharmaceuticals	Phase II Genotype 1 Treatment-naive Up to 48 weeks	Being studied with PEG-IFN/RBV

Agent/Dose/Sponsor	Phase/Population/Duration	Comments
asunaprevir (BMS-650032) 200 mg Once-daily Bristol-Myers Squibb	Phase II and Phase III Genotype 1 Treatment-naive 12–48 weeks Genotypes 1 and 4 Treatment-naive 24–48 weeks Genotype 1b Treatment-naive Interferon-ineligible/intolerant Treatment-experienced (null responders) 24 weeks Genotypes 1, 2, 3, and 4 Treatment-experienced (PEG-IFN/RBV control arm in BMS clinical trial) 24 weeks Genotypes 1 and 4 Treatment-experienced (partial- and null responders) 24 weeks	Being studied + peginterferon lambda (BMS-914143) + peginterferon lambda and RBV + daclatasvir (BMS-790052, an NS5a inhibitor) + daclatasvir and BMS-791325 (non-nucleoside polymerase inhibitor) + daclatasvir with peginterferon lambda and RBV + daclatasvir with PEG-IFN/RBV (as quad or as rescue) Quad in null responders not open as of 6/12
BI 201335 120 mg, 240 mg Once-daily Boehringer Ingelheim	Phase II and phase III Genotype 1 Treatment-naive 4–48 weeks Genotype 1 Treatment-naive and treatment-experienced (relapsers) 24 or 48 weeks Genotype 1 Treatment-experienced (partial- and null responders, and relapsers) 24 or 48 weeks	Being studied + PEG-IFN/RBV + BI 207127 (non-nucleoside polymerase inhibitor) + BI 207127 and RBV + BI 207127 with PEG-IFN/RBV Treatment-naive/relapse study not open as of 6/12

TABLE 8. Protease Inhibitors in Phase II and III (Cont.)

Agent/Dose/Sponsor	Phase/Population/Duration	Comments
danoprevir/r (RG7227) 100 mg (boosted with 100 mg of ritonavir) Twice-daily; fixed-dose combination is in phase I Hoffmann-La Roche/ Genentech	Phase II Genotype 1 Treatment-naive 24 or 48 weeks Genotypes 1 and 4 Treatment-naive Up to 48 weeks Genotypes 1 and 4 Treatment-naive or interferon-ineligible/intolerant 24 weeks Genotype 1 Treatment-experienced (partial- or null responders) 24–48 weeks Genotypes 1 and 4 Treatment-naive or treatment-experienced (null responders) with cirrhosis 24 weeks Genotype 1 Treatment-experienced (with protease inhibitors) 24-26 weeks	Being studied + PEG-IFN/RBV + mericitabine (RG7128, a nucleoside polymerase inhibitor) + mericitabine and RBV + mericitabine with PEG-IFN/RBV Trial in protease inhibitor-experienced not open as of 6/12
GS-9256 75 mg, 150 mg Twice-daily Gilead Sciences	Phase II Genotype 1 Treatment-naive Up to 48 weeks Genotype 1 Interferon-ineligible/intolerant	Being studied + PEG-IFN/RBV + tegobuvir (GS-9190, a non-nucleoside polymerase inhibitor) and RBV

Agent/Dose/Sponsor	Phase/Population/Duration	Comments
GS-9451 200 mg Once-daily Gilead Sciences	Phase II Genotype 1 Treatment-naive IL28B CC genotype only 6–12 weeks Genotype 1 Treatment-naive Up to 48 weeks Genotype 1 Treatment-naive 12–24 weeks Genotype 1 Interferon-ineligible/intolerant 24 weeks Genotype 1 Treatment-experienced (breakthrough, partial- and null responders, and relapsers) 24–48 weeks	Being studied + PEG-IFN/RBV + tegobuvir (GS 9190, a non-nucleoside polymerase inhibitor) and RBV + GS-5885 (NS5a inhibitor) and tegobuvir + GS-5885 and RBV + GS-5885 and tegobuvir with RBV + GS-5885 with PEG-IFN/RBV + GS-5885 (with PEG-IFN/ RBV "rescue" arm)
MK-5172 Various doses studied, reduced to 100 mg/day 100 mg (800 mg in 7-day monotherapy trial only) Once-daily Merck	Phase I and phase II Genotype 1 Treatment-naive or treatment-experienced, and Genotype 3 (must be treatment-naive) 7 days Genotype 1 Treatment-naive 24 or 48 weeks	Being studied as monotherapy + PEG-IFN/RBV

TABLE 8. Protease Inhibitors in Phase II and III (Cont.)

Agent/Dose/Sponsor	Phase/Population/Duration	Comments
simeprevir (TMC435) 150 mg (100 mg dose studied in Japan) Once-daily Janssen Pharmaceuticals/ Tibotec/Medivir	Phase II and phase III Genotype 1 Treatment-naive 24 or 48 weeks Genotype 1 Treatment-naive or treatment-experienced (relapsers) 24 or 48 weeks Genotype 4 Treatment-naive or treatment-experienced (partial responders or relapsers) 24 or 48 weeks (treatment-naive) 48 weeks (treatment-experienced) Genotype 1 Treatment-experienced (null responders; some with bridging fibrosis and cirrhosis) 12–24 weeks Genotype 1 Treatment-experienced (partial- and null responders) 48 weeks Genotype 1 Treatment-experienced (participants given placebo or ≤14 days of DAA treatment in earlier trials) 24 or 48 weeks	Being studied + PEG-IFN/RBV + GS-7977 (formerly PSI-7977, a nucleotide polymerase inhibitor) + GS-7977 and RBV
vaniprevir (MK-7009) 300 mg Merck Twice-daily	Phase III	Being developed in Japan only

TABLE 9. Non-Nucleoside Polymerase Inhibitors in Phase II and III

Agent/Dose/Sponsor	Phase/Population/Duration	Comments
ABT-072 400 mg Once-daily Abbott Laboratories	Phase II	No new studies listed
ABT-333 400 mg Twice-daily Abbott Laboratories	Phase II Genotype 1 Treatment-naive 12 weeks Genotype 1 Treatment-naive and treatment-experienced (non-responders) 12 weeks Genotype 1 Treatment-naive or treatment-experienced (null responders) Up to 24 weeks	Being studied + ABT-450/r (ritonavir-boosted protease inhibitor) and RBV + ABT-450/r and ABT-267 (NS5a inhibitor) + ABT-450/r and ABT-267 with RBV
BI 207127 600 mg Twice-daily Boehringer Ingelheim	Phase II Genotype 1 Treatment-naive 16 to 40 weeks	Being studied + BI 201335 (protease inhibitor) + BI 201335 and RBV + BI 201335 with PEG-IFN/RBV
BMS-791325 75 mg, 150 mg Twice-daily Bristol-Myers Squibb	Phase II Genotype 1 Treatment-naive 12–24 weeks Genotype 1 Treatment-naive or treatment-experienced (<4 weeks of treatment only) 4–48 weeks	Being studied + PEG-IFN/RBV + asunaprevir (BMS-650032, a protease inhibitor) and daclatasvir (BMS-790052, an NS5a inhibitor)
setrobuvir (ANA598) 200 mg Twice-daily Anadys/ Hoffmann-La Roche	Phase II Genotype 1 Treatment-naive or treatment- experienced (breakthrough, partial and null responders, relapsers) 28 weeks (treatment-naive) 48 weeks (treatment-experienced)	Being studied with PEG-IFN/RBV

TABLE 9. Non-Nucleoside Polymerase Inhibitors in Phase II and III (Cont.)

Agent/Dose/Sponsor	Phase/Population/Duration	Comments
tegobuvir (GS-9190) 20 mg, 30 mg, 40 mg Twice-daily Gilead Sciences	Phase II Genotype 1 Treatment-naive 16-48 weeks Genotype 1 Treatment-naive (interferon-ineligible only) or treatment-experienced (interferon-intolerant only) 24 weeks Genotype 1 Treatment-experienced (breakthrough, partial- or null responders, and relapsers) 24 weeks or 24–48 weeks	Being studied + GS-9526 (protease inhibitor) with PEG-IFN/RBV + GS-9451 (protease inhibitor) with PEG-IFN/RBV + GS-5885 (NS5a inhibitor) and GS-9451 + GS-5885 and GS-9451 with RBV
VX-222 (formerly VCH-222) 400 mg Twice-daily (coadministered with 1125 mg of telaprevir twice-daily) Vertex Pharmaceuticals	Phase II Genotype 1a only Treatment-naive 12 or 16 weeks Genotype 1 Treatment-naive 12, 24, or 36 weeks Genotype 1 Treatment-naive or treatment-experienced (partial- or null responders, and relapsers) with cirrhosis 24 or 48 weeks	Being studied + telaprevir (protease inhibitor) and RBV + telaprevir with PEG-IFN/RBV Study in Genotype 1a not open as of 6/12

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HEPATITIS C (HCV) TREATMENT ACCESS: SPOTLIGHT ON THAILAND/ASIA

By Karyn Kaplan

According to the Universal Declaration of Human Rights and subsequent treaties, all people have a fundamental right to the highest attainable standard of health, as well as a right to the benefits of scientific progress and its applications. Yet many governments in the global South are unable to even progressively provide these rights to their people. Excessive patent protections and the high price of drugs, especially for people in the global South, make the prospect of groundbreaking new treatments, such as those in the hepatitis C pipeline, bittersweet. The promise of new medications is meaningless in much of the world where there is no access. The following story describes a unique partnership between activists in the global North and South, first introduced by a harm reduction activist on the Lower East Side, to overcome this cruel reality.

For decades, Thailand's dual HIV and HCV epidemics raged among people who inject drugs, with prevalence rates of 50% and 90%, respectively. But the government chose to ignore the crisis, denying proven prevention and treatment interventions. In 2002, Paisan Suwannawong, an HIV-positive injecting drug user (IDU), and New York-based AIDS activist Karyn Kaplan founded Thai AIDS Treatment Action Group (TTAG) to respond to this government neglect. TTAG took up the fight against HIV-related discrimination at the policy and program levels by providing information, trainings on leadership, and advocacy skills to people living with, and at risk for, HIV and hepatitis C.

In the 1990s, Thailand had become a global role model in addressing sexual transmission of HIV, due in large part to civil-society involvement in its public-health response. Yet this did not translate to success among marginalized and criminalized populations. The government denied the provision of clean injecting equipment to drug injectors, who faced extreme social exclusion. Methadone programs did not adhere to international standards; participants were forced to taper off methadone unsuccessfully three times before they were eligible for maintenance therapy. People who use drugs were often forced to quit in order to receive health care, and for years were denied antiretroviral therapy.

Historic Global Fund Grant for Harm Reduction

In 2002, the same year they cofounded TTAG, Paisan Suwannawong and Karyn Kaplan helped to establish the Thai Drug Users' Network (TDN). As the founding chairman of TNP+ (Thai Network of People Living with HIV/AIDS), a group focused on advocating for universal access to treatment for HIV/AIDS, Suwannawong applied his activist skills to highlight and help bridge gaps in HIV treatment access for this marginalized group.

One of TTAG's first major successes was to secure funding from the Global Fund to Fight AIDS, TB and Malaria (GFATM) for peer-driven harm reduction. TTAG chose to bypass the traditional "country coordinating mechanism" because then–Prime Minister Thaksin Shinawatra's government was waging its most repressive drug war, in which tens of thousands of people were forced into drug "treatment" centers, blacklisted, and arbitrarily arrested (and worse). With this funding, TTAG established Thailand's first program to provide comprehensive HIV prevention services to people who use drugs.

While the project helped establish some much needed infrastructure for HIV services for people who use drugs, wide swathes of the country did not have syringe exchanges, peer outreach, education and counseling programs, or drop-in centers. The government remained inert, torn between compelling public health evidence and political hostility. Meanwhile, drug users themselves were organizing advocacy networks to bolster efforts at the national level.

Hepatitis C Emerges as a Priority

Issues emerging out of peer outreach efforts included police harassment and abuse, discrimination in the health care setting, and a lack of information on overdose and hepatitis C coinfection; HIV was simply one of a litany of daily problems faced by people using drugs. In response, TTAG established various projects, such as: a human rights documentation and training initiative, an overdose prevention and management project, and an HIV/HBV/HCV coinfection education and advocacy project (the "Coinfection Project"). The Coinfection Project began in 2007 as the drug user community was seeing increasing numbers of peers getting sick and dying from untreated chronic hepatitis C, and those coinfected with HIV were not being prescribed the best available HIV treatment regimen.

Empowerment through Education: A TTAG/TAG Collaboration

Thailand had community advocates desperate for information; TAG had the scientific expertise, with a unique activist bent that lent itself to adaptation for community-driven advocacy initiatives. In 2007, TTAG invited Tracy Swan, TAG's Hepatitis/HIV Project Director, to Thailand. Her job was to help map the problem, consult with people who use drugs and people living with HIV/AIDS at regional workshops to understand—and to answer—their questions and concerns about HCV.

First, Swan accompanied Suwannawong and Kaplan to Bangkok, Chiang Mai, and Had Yai, three hot spots of drug injection and HIV/HCV in Central, Northern and Southern Thailand, to address community questions and concerns about HCV. It was clear that, from an informational standpoint, the affected community was starting at point zero: despite astronomical prevalence, the government had simply ignored the problem, and no screening, prevention or treatment programs were in place. Community questions were basic: "Can hepatitis B virus (HBV) turn into hepatitis C?" "If you're poor, can you get treatment?" "How can hepatitis C be prevented?" and "Is it a disease of the kidneys?" Others had never heard of the hepatitis C virus.

At the same time, TTAG and TAG codeveloped a "Standard of Care" survey to find out if—and which—viral hepatitis diagnostics and services were offered at health care centers and hospitals around Bangkok; what they cost; and whether or not people with HIV/AIDS and people who use drugs would be eligible. The survey also examined barriers to provision of these services, such as lack of information or reluctance among providers.

Ultimately, the TTAG/TAG consultations generated a community-based, peer-led advocacy strategy similar to the one that was successful with HIV. Tracy Swan worked with Lei Chou, TAG's HIV/Hepatitis Project Coordinator, to weave survey results, questions, concerns, and gaps in access to viral hepatitis services into an HIV/HBV/HCV Education and Advocacy curriculum[1] for peer educators, focusing on IDU-specific issues. The curriculum was translated into Thai by Anusorn Quamman, a meticulous translator deeply familiar with TTAG's work and specifically trained in medical translation, and reviewed by the communities consulted as well as specialist clinicians in Thailand and the United States. In 2009, the curriculum was piloted for 30 activists at a four-day national-level training workshop held in Cha-am district on the eastern seaboard.

Setting up a National-Level Movement

Activists in Thailand knew from their HIV/AIDS treatment advocacy campaign, which led to antiretroviral therapy (ART) being covered under universal health care, that information and education were not enough. First, a critical mass of informed people must get educated; then, an action plan must be developed to push urgent priorities onto local and national policy agendas. TTAG mobilized financial support from key donors who were interested in contributing to a stronger response to the problem of viral hepatitis coinfection among Thailand's drug users and people living with HIV/AIDS.

Over the next few years, TTAG cultivated additional funding to educate hundreds of people who use drugs and people living with HIV/AIDS across Thailand about viral hepatitis and HIV. By the end of 2011, TTAG's Coinfection Project had trained six teams of four HIV/HCV peer educators in three regions of Thailand (North, Northeast, and Central), more than 200 people living with HIV/AIDS, and 60 IDUs. In 2012, the Coinfection Project expanded to include the South. In each region, TTAG nurtured more trainers and funding was channeled to local groups of HIV-positive people to continue the movement at the local and provincial level.

TTAG's cadre of coinfection advocates identified access to testing as the first step to establishing demand for treatment. In response to the lack of access to HCV diagnostics and treatment, the Coinfection Project's manager, Kamon Uppakaew, organized the Project's first peer-led research initiative in 2011. This study was designed to assess barriers to HCV diagnostics and treatment, and inform strategies to improve access. TTAG, with technical assistance from colleagues at the HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT)/Thai Red Cross, developed a research protocol and questionnaire, and surveyed 153 people living with HIV/AIDS across the country. Dr. Anchalee Avihingsanon, Thai HCV expert and clinical researcher at HIV-NAT, and her team set up a database for longer-term data collection by TTAG's peer researchers. Dr. Anchalee is helping TTAG to analyze the data they have already collected, adding to the growing body of local evidence supporting HCV treatment access.

The Last Frontier: From Evidence to Action

Finally, the policy barriers had to be addressed. In 2010, TTAG's International HIV/HCV Campaigner, Noah Metheny, Esq., helped to develop policy materials. These included an information sheet with price comparisons of pegylated interferon (PEG-IFN), ribavirin (RBV), HCV diagnostic and administrative costs

across six countries in Asia, and a Thailand-specific policy brief on injecting drug use and HIV/HCV coinfection. The policy brief summarized the national situation and community demands, including the following:

- scale up evidence-based harm reduction and needle and syringe programs (NSP) for HCV prevention;
- provide access to universal HCV testing for HIV-positive IDUs;
- develop HCV treatment guidelines for the Thai context based on international best practice;
- support the Thai Government Pharmaceutical Organization (GPO) to produce or import generic versions (biosimilars) of PEG-IFN; and
- increase political support for utilizing "TRIPS flexibilities"[2] to expand access to cheaper treatment.[3]

TTAG's advocacy continued: on World Hepatitis Day, July 28, 2011, TTAG enjoined regional branches of the Thai Network of People Living with HIV/AIDS (TNP+) to help mobilize over 150 HIV-positive people, who participated in an action at the National Health Security Offices (NHSO), Thailand's largest payer of health care. TTAG and TNP+ demanded coinfection treatment guidelines, better public-health leadership, better HIV treatment for coinfected people, and free HCV testing and treatment. During the demonstration, activists met inside the NHSO with its secretary general, Dr. Winai Sawasdivorn, and two doctors representing the HIV and liver-disease divisions of the agency, to discuss activist demands. The government officials promised to explore options for improving access to treatment for coinfected people, such as providing HCV testing to all HIV-positive people, and offering better first-line ART options for people coinfected with HIV/HCV. Meanwhile, outside, demonstrators chanted, talked with media, and carried signs declaring, "HCV=Death," "Pegylated Interferon=Expensive!" and "Why isn't the Thai government doing anything about Hepatitis C?"

Other advocacy efforts, such as regular meetings with key individuals and agencies from government, industry, and civil-society groups such as HIV-NAT, the Thai GPO, Médecins Sans Frontières (MSF), and Merck (MSD)-Thailand proved fruitful, particularly in terms of sharing information that leads to better advocacy strategies.

Last year, the GPO traveled to Viet Nam to determine whether or not to import cheaper PEG-IFN, which was being produced there, demonstrating a clear commitment to future access. Unfortunately, the producer of the purported biosimilar product was unable to provide the necessary safety and efficacy data for consideration by the Thai entities for import. HIV-NAT is committed

to implementing clinical trials, including among coinfected people, to help ensure access to treatment and contribute to the body of knowledge on HCV treatment safety, efficacy, and outcomes in Thai people. TTAG met with Merck (MSD)-Thailand to discuss price reduction negotiations, to ask directly whether and how much their prices for PEG-IFN and ribavirin, as well as their HCV protease inhibitor, boceprevir, would be reduced so the Thai government could afford to put it on their National Essential Drugs List and pay for universal coverage for those who need it.

Thailand: Leader in HIV Treatment Access, also for HCV?

Merck confirmed that significant price reductions had been agreed upon in negotiations and that they had signed a formal agreement with the Thai government. As a result, the Thai government will include PEG-IFN and ribavirin on the National Essential Drugs List in 2012, so that they can be provided free under Thailand's universal health care coverage scheme. Although the government indicated its intention to limit treatment initially to people infected with HCV genotypes 2 and 3,[4] TTAG will push to broaden eligibility criteria, especially since the IL28B CC genotype is common among Asians and associated with a higher likelihood of cure in people with HCV genotype 1.

While Thai activists are heartened by progress, until doctors can and will prescribe treatments for people who need it, the struggle continues. "We need to make sure people are supported on treatment, and that we continue to fight for access to newer, better treatments when they become available," said Paisan Suwannawong, TTAG's Executive Director. "I was lucky to get treatment through a donation abroad and cure my hepatitis, but I will keep advocating until everyone in my country has the same opportunity."

HCV Activism Reaching across Asia

Asia is home to 130 million of the world's 160 million people living with chronic hepatitis C. Drug-user activists are increasingly developing advocacy strategies and activities to respond to the utter lack of treatment access. Bangkok is home to many regional HIV and harm reduction networks, comprising thousands of directly affected people. The Asia Pacific Network of People Living with HIV/AIDS (APN+) and the Asia Network of People who Use Drugs (ANPUD) are natural allies in the push for HCV treatment. Early on, TTAG reached out to these regional networks to gauge interest in working

together to expand HCV treatment access for all. TTAG, APN+, ANPUD, MSF, Seven Sisters Asia Pacific Coalition (7S), and World AIDS Campaign formed a coalition, meeting regularly to share information and strategize about policy advocacy. One of the first initiatives to emerge from this collaboration was the First South and Southeast Asia Regional Community Meeting on HIV/Hepatitis C Coinfection.

A meeting of two dozen HIV and harm reduction activists from China, Nepal, Vietnam, Thailand, India, and Indonesia was held in Bangkok in June 2010. The meeting included country situation presentations, a review of barriers to HIV/HCV diagnostics, discussion of treatment and care with a focus on intellectual property issues, and advocacy strategizing (including resource mobilization and coalition building). A web-based listserv was set up to broaden participation in the ongoing discussion. A summary report was made public.[5] Many of the workshop participants wanted to translate the TTAG/TAG coinfection manual into local languages, such as Vietnamese and Nepalese, to conduct their own peer education.

HCV activism continues to gain momentum. In India, where the bulk of the world's generic HIV medications are sourced, groups of HIV-positive activists are organizing advocacy initiatives to bring much-needed attention to the twin crises of HIV and HCV, in particular among injectors. In February 2012, activists in Manipur, a region of India bordering Burma where injecting is prevalent and HIV/HCV rates high, sent a letter to Anand Grover, UN Special Rapporteur on the Right to Health. They requested that he investigate the Indian government's lack of action in the face of this health crisis and publicly denounce what they felt was tantamount to the denial of the right to health and life.

In 2011, at the International Congress on AIDS in Asia and the Pacific (ICAAP) in Busan, South Korea, ANPUD led a rally targeting WHO Director-General Margaret Chan's failure to respond to demands for increased leadership and resource commitments for HCV despite the World Health Assembly resolution in 2010 prioritizing viral hepatitis as an urgent global health concern. Dean Lewis, coordinator of ANPUD, pointed out, "Although hepatitis C is a curable disease, the medications are prohibitively expensive and out of the reach of the majority of those infected."

Ensuring that treatment for HCV and HIV reaches everyone who needs it is the challenge of the decade. If HIV activism is an accurate bellwether, activists in Asia will broaden access to HCV diagnostics and treatment in the region and help to pioneer a global movement. Global North/South partnerships such as

the one between TAG and TTAG serve as a model of collaboration for effective advocacy. Locally designed, creative solutions will also emerge. Many of the same battles on intellectual property issues such as patent protections and Big Pharma pricing policies will have to be waged—and won. The slow, hard work of peer-driven community education and activism is an integral part of the battle.

As soon as affordable treatment is within reach, civil-society networks should push HCV onto the national public-health agenda to get the resources and attention it deserves and to ensure access is equitable. Community advocates will need to join forces with providers to develop appropriate support systems for people on treatment. The work is not simple, but much of it has been done before, with HIV/AIDS. The light at the end of the tunnel is that, for HCV, we have a cure.

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2. "TRIPS (Trade-Related Aspects of Intellectual Property Rights) flexibilities" refers to the ability of World Trade Organization member countries to retain policy options, flexibilities, and safeguards, such as compulsory licensing, when being required to enforce or protect intellectual property rights. For more information: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2049_PolicyBrief_TRIPS_en.pdf.
3. TTAG's Thai and English-language educational and advocacy materials are available at http://www.ttag.info.
4. In Thailand, genotypes 1, 3 and 6 are prevalent, and genotypes 2 and 3 are easier to treat than other genotypes.
5. The summary report is accessible here: http://www.ttag.info/pdf/Final%20Report_Regional%20HCV%20meeting-1.pdf.

THE TUBERCULOSIS DIAGNOSTICS PIPELINE

By Colleen Daniels and Coco Jervis

Introduction

Accurate tuberculosis (TB) diagnosis has the potential to be the cornerstone of all global TB control efforts. However, the poor accuracy of the most commonly used test, sputum smear microscopy, and the weeks-long time to results of the previously prevalent gold standard for TB diagnosis of culture growth, have combined to make accurate diagnosis the Achilles's heel of efforts to eradicate TB. The World Health Organization (WHO) estimates that one-third, or almost 3 million, of the world's 8.8 million TB cases are never detected or reported let alone diagnosed, treated, and cured properly.[1] The most commonly used TB tests involve a trade-off between insensitive assays such as microscopy, which detects only 50% of all TB cases, and fewer in children or people with HIV, and accurate ones (such as culture) that require weeks of in vitro growth before generating results, meaning that people with possible TB must come back to the lab weeks later to begin appropriate treatment. In some places such as the private sector in India, people are often given ineffective and expensive TB antibody tests that combine uselessness with profits to the lab owners, with no benefit to the patient. These barriers ensure that many patients are neither diagnosed nor treated properly.

The past decade has seen both the rollout to developing countries of existing technologies such as rapid liquid culture and the development of new molecular (DNA-detecting) technologies such as the Hain Lifescience (Germany) GenoType MTBDR*sl* and the Cepheid (United States) GeneXpert that detect both the presence of TB and common resistance mutations to isoniazid and rifampicin. This progress, however, must be tempered by the recognition that we still do not have a low-cost, laboratory-free point-of-care (POC) test for TB.[2] We have seen how POC tests for "HIV and malaria have completely transformed the management of these diseases,"[3] and we now wait impatiently for one to change the management of TB.

The need for simpler methods to accurately diagnose TB in everyone including children and people with immune suppression such as HIV cannot be overstated—the faster a patient is screened, the quicker treatment can be initiated, ultimately reducing morbidity and reducing the spread of TB.[4]

Increased funding for TB research and development is still desperately needed in order to maximize the breadth and depth of innovative technologies currently

being considered in the TB diagnostic pipeline. Funding for TB diagnostics research was a minimal US$44.6 million in 2010,[5] compared to the US$340 million the Global Plan to Stop TB indicates is needed annually.[6]

Factors essential for an improved TB diagnostic test

The utility of a test is defined by the following factors linked to test accuracy and the place within the health system where the test is likely to be used.

Sensitivity: The ability of the test to accurately identify people with the disease. Low sensitivity of a test will cause people who have the disease to not be identified, not get appropriate treatment, suffer due to disease progression, and transmit the disease to others.

Specificity: The ability of the test to accurately identify people who do not have the disease. Low specificity means that more people who do not have the disease will wrongly be identified as having it, leading to inappropriate treatment.

Impact of test results on clinical decisions and patient outcomes: Sensitivity and specificity are surrogates for a test's ability to improve treatment outcomes. Even a highly sensitive and specific test may not result in improved treatment decisions or reduce morbidity and mortality if it takes too long to provide results, thus failing to allow prompt initiation of proper treatment.

Diagnostic algorithm: An algorithm is a recommended sequence in which procedures such as symptom screens can be combined with tests in a diagnostic pathway. The most efficient programs strive to integrate procedures and tests to ensure the most rapid, accurate, and rational diagnosis and treatment for all patients.

Health posts: These are the most decentralized locations of the health system, serving 60% of TB patients. They often lack access to electricity, water, or trained laboratory staff, and do not support diagnostic or biosafety equipment.

Peripheral laboratories or health centers: These include district hospitals and laboratories and serve 25% of people in need of TB services. They have trained staff and the capacity to conduct sputum smear microscopy, but only inconsistent electricity and minimal biosafety capacity.

Reference laboratories with sophisticated test procedures are accessible to only 15% of those in need of TB services. They have highly skilled staff, reliable electricity and water supply, can ensure biosafety, and can conduct culture and nucleic acid amplification tests (NAATs).

Source: 2011 Pipeline Report.[9]

As a result of these continuing discussions, this year's pipeline is structured by the diagnostic test technology: culture, molecular, and non-molecular.

The TB Diagnostics Pipeline

Test	Sponsor	Type/Sample	Status	Comments
Culture-based technologies				
TREK Sensititre MYCOTB MIC plate	Thermo Fisher Scientific	A dry microdilution plate containing lyophilized antibiotics	Proof of principle completed	The MYCOTB plate is intended for determination of MICs to first- and second-line TB drugs
MDR-XDRTB Color Test	FIND	Rapid colorimetric drug susceptibility test (DST)	Proof of principle completed. Feasibility study to commence	A thin layer agar method to detect TB and screen for isoniazid-, rifampicin-, and ciprofloxacin-resistance is being developed in a kit format
Molecular-based technologies				
Loopamp	FIND/Eiken Chemical Co., Ltd.	Loop mediated isothermal amplification (LAMP) for TB	Evaluation and demonstration phase	Reviewed by WHO expert group in April 2012; no recommendation forthcoming
GenoType MTBDR*sl* line probe assay (LPA), second-line	FIND/Hain Lifescience	Detects genetic mutations associated with resistance to fluoroquinolone (FQ) antibiotics, and the second-line injectable drugs, amikacin (AK), kanamycin (KN), and capreomycin (CP)	Field studies conducted	Reviewed by a WHO Expert Group in 2012; no public recommendation or discussion at the Strategic and Technical Advisory Group for Tuberculosis (STAG) meeting in June 2012
Non-molecular-based technologies				
TBDx	Signature Mapping Medical Sciences, Inc.	Automated system for smear microscopy	Field studies conducted	Automated slide loading and reading
Alere Determine TB-LAM Ag lipoarabinomannan (LAM) lateral flow test	Alere	Lateral flow test for diagnosis of TB in adults with HIV infection	Field studies conducted	Field study of a urine dipstick assay of a LAM protein completed. It was compared to a Clearview ELISA laboratory-based test and found to have acceptable sensitivity and high specificity for people living with HIV who had <100 CD4 cells and TB disease

Culture Technologies

The most widely used technology to diagnose TB is acid-fast bacilli (AFB) sputum smear microscopy. It is rapid and inexpensive, but has low sensitivity, particularly in people living with HIV (PLHIV). It also does not provide drug susceptibility information, and performance of the test depends on the operator.[10,11] Liquid culture media are more sensitive and faster than traditional techniques, which use egg-based solid media. However, culture using thin layer synthetic agar (which uses a solid medium and is based on the microscopic detection of early mycobacterial growth)[12] does improve performance of solid culture media.[13] Liquid culture systems reduce delays in getting results, and for DST the result can be obtained in less than 10 days compared to 28–42 days for solid media.[14] Liquid systems have more issues with contamination and require a strong network of quality-assured microscopy in countries. The WHO recommends the use of TB liquid culture and DST in low-income settings and implementation of these systems as part of national laboratory strengthening plans.[15]

There are two culture-based technologies in the pipeline: the TREK Sensititre MYCOB MIC plate and the solid culture MDR/XDR Color Test.

TREK Sensititre MYCOTB MIC Plate

The TREK Sensititre MYCOTB MIC (Trek Diagnostic Systems, Thermo Fisher Scientific, United States) plate is intended for determination of drug resistance to first- and second-line TB drugs. A multisite study was conducted by the TB Clinical Diagnostics Research Consortium (CDRC) to evaluate the diagnostic accuracy of the MYCOTB plate compared to the reference agar proportion method (APM). Two reference TB laboratories, one in South Korea and one in Uganda, conducted the study.

A presentation by Dr. Susan Dorman[16] at the Keystone Symposium on Drug Resistance and Persistence held in Uganda in May 2012, compared APM with TREK in archived *Mycobacterium tuberculosis* (MTB) clinical strains from South Korea and Uganda with previously characterized DST patterns were used. A "total of 228 MTB isolates were selected, among which 69 (30%) had previously been characterized as MDR-TB and 52 (23%) had been characterized as XDR-TB. The MYCOTB plate showed ≥95% concordance with APM for all tested drugs except ethionamide 5.0 ug/mL (94.0%), rifabutin (92.4%), moxifloxacin 0.5 ug/mL (87.3%), and moxifloxacin 2.0 ug/mL (81.0%) in interim results. MYCOTB plate interpretation by two independent readers showed ≥96% agreement for all tested drugs."[17]

Solid Culture MDR-XDRTB Color Test

A thin layer agar method[18] (TLA) to detect TB and screen for isoniazid-, rifampicin-, and ciprofloxacin-resistance is being developed in a kit format by the Foundation for Innovative New Diagnostics (FIND) and the London School of Hygiene & Tropical Medicine (LSHTM). The color test makes it possible to perform sputum smear and culture plate inoculation and incubation safely in basic regional laboratories that currently provide only sputum microscopy, with biosafety requirements that are similar to those for smear microscopy. Two drops of a sample are dropped onto selective thin layer agar for incubation in room air, resulting in MDR-TB (multidrug-resistant TB) testing and XDR-TB (extensively drug-resistant TB) screening.[19]

FIND and LSHTM established proof-of-concept for this approach. A prospective feasibility study using sputum is now ready for enrolment, and will be conducted in a regional laboratory in Brasov, Romania, and in a referral laboratory in Lima, Peru. The study aims to evaluate the operational feasibility of using sputum from TB suspects, and will compare performance of the color test for TB- and resistance-detection against the automated mycobacteria growth indicator tube (MGIT) system and the Löwenstein-Jensen (LJ) culture systems.[20]

Molecular-Based Technologies

Molecular-based detection of TB includes the use of nucleic acid amplification tests (NAATs), which are specific and reliable. Test results are normally available within 24 to 48 hours—and sometimes within two hours—of receipt of sample, compared to culture, which takes weeks.[21] Sensitivity, however, is variable, especially in smear negative and extrapulmonary samples.

Line probe assay technology used to detect MDR-TB involves extracting DNA from MTB isolates or directly from clinical specimens. Polymerase chain reaction (PCR) amplification of the resistance-determining region of the gene is performed. The readout shows whether the sample contains MTB and whether defined resistance sequences are present.[22]

Manual Isothermal NAAT for TB (LAMP)

FIND (Switzerland) and Eiken Chemical Co., Ltd. (Japan) are developing a loop-mediated isothermal amplification (LAMP) technology for TB detection in sputum using a relatively convenient kit format (Loopamp) with a simple visual readout. Evaluation and demonstration study phases were completed in 2011

at three sites in India, Uganda, and Peru. The Indian results were discordant with the other two and with test specifications. As a result, the phase I demonstration study will be redone to prove/disprove the hypothesis that the cause of the different results was due to a need for greater training. Eiken and FIND will redo the evaluation study at all sites (South Africa, Vietnam, Brazil, and Peru) to include the updated training module.[23] The new device includes a specially designed sputum-transfer device to ensure that appropriate volumes of sputum will be supplied with the finished kit. While a WHO expert group reviewed the data on LAMP and Loopamp in April 2012, no public recommendation or discussion occurred at STAG in June.

Molecular Detection of Drug Resistance

GenoType MTBDR*sl*

Based on the already-approved GenoType MTBDR*plus*, which detects common isoniazid- and rifampicin-resistance-associated mutations, the Hain PCR-based assay GenoType MTBDR*sl* allows for the simultaneous detection of TB organism and its resistance to fluoroquinolones, aminoglycosides/cyclic peptides, and ethambutol.[24] It is used to detect XDR-TB. Several studies have assessed this test.

At four sites in Eastern Europe, Ignatyeva et al.[25] evaluated the performance of the Genotype MTBDR*sl* assay compared to that of phenotypic drug susceptibility testing (Becton Dickinson's BACTEC MGIT 960 system). Sensitivity for the detection of resistance to fluoroquinolones, ethambutol, amikacin, and capreomycin varied between 77.3% and 92.3% and was much lower for kanamycin at 42.7%. The sensitivity for the detection of XDR-TB was 22.6%, and test specificity was over 82% for all drugs.[26]

In South Africa, Said et al.[27] found that the sensitivity and specificity of the GenoType MTBDR*sl* assay were, respectively, "70.3% and 97.7% for ofloxacin, 25.0% and 98.7% for kanamycin, 21.2% and 98.7% for capreomycin and 56.3% and 56.0% for ethambutol."[28] The assay performed well for ofloxacin, was less sensitive for kanamycin- and capreomycin-resistance, and had low sensitivity and specificity for ethambutol-resistance.

The study conducted in Eastern Europe concluded that the sensitivity for the detection of kanamycin-resistance needs improvement, and the South African study recommended that the GenoType MTBDR*sl* assay include additional genes to achieve better sensitivity for all the drugs tested.

Last year, a WHO Expert Group (EG) considered data from this and unpublished studies and determined that the available data supported a recommendation for use of the assay testing culture isolates, but that it could not endorse the use of the assay for direct testing on sputum specimens because there were too few data on direct testing available. As a result, FIND and Hain Lifescience GmbH (developer and manufacturer) implemented further studies of direct testing. These data on the GenoType MTBDRs*l* test were presented to a WHO EG in April 2012. Neither a recommendation nor a public explanation of the current WHO evaluation of this test were available publicly as this report went to press.[29,30]

Non-Molecular Diagnostic Technologies

Biomarkers are biologic features that can identify and/or be used to monitor a physiological process or disease in the host. Nahid et al. reported that several new approaches to discovery of TB diagnostics biomarkers are now being researched with a focus on pathogen-specific or host-based markers. Researchers have screened urine, serum, saliva, and breath in the search for markers that can be evaluated via a variety of platforms including genomic, proteomic, metabolomic, lipidomic, and glycomic.[31]

TBDx

TBDx (Signature Mapping Medical Sciences, Inc., a subsidiary of Applied Visual Sciences, Inc., United States) is an automated system for smear microscopy that automatically loads and reads slides. It autofocuses and digitally captures images and uses computerized algorithms to count AFBs and classify slides as positive or negative.[32]

At the 2012 Conference on Retroviruses and Opportunistic Infections (CROI), Dr. Gavin Churchyard presented results of a study, conducted by the Aurum Institute (South Africa) and Guardian Technologies International (United States), using culture as the control.[33] It concluded that the sensitivity of TBDx is very good, but specificity is too low, when used as a fully automated system. Test results by a microscopist showed sensitivity of 52.8% and specificity of 98.6% compared to TBDx, which had sensitivity of 75.8% and specificity of 43.5%. However, Dr. Churchyard also showed that TBDx tends to overread, which leads to high false-positivity. He concluded that it is a promising technology that merits further optimization and evaluation.

Alere Determine TB-LAM Ag

Alere Determine TB-LAM Ag (Alere, United States) is a lateral flow test for detection of urinary lipoarabinomannan (LAM).[34] The LAM protein is shed from TB bacteria in people with TB disease.

Lawn et al. in South Africa assessed the diagnostic accuracy of the Alere Determine TB-LAM Ag for screening for HIV-associated pulmonary tuberculosis before antiretroviral therapy (ART). Their study found that it had acceptable sensitivity and very high specificity for people with TB disease who also had CD4 counts <100. These results did not differ statistically from the sensitivities obtained by testing a single sputum sample with the Xpert MTB/RIF assay.[35]

Peter et al.[36] found that LAM combined with smear microscopy was able to rule in TB in 71% of MTB culture-positive patients. This indicates that the LAM strip test may be a potentially useful rapid rule-in test for TB in hospitalized patients with advanced immunosuppression.

Dr. Susan Dorman presented a study at CROI 2012[37] which found that the Alere Determine TB-LAM Ag, which detected TB in two-thirds of TB patients with CD4 counts <100, may be a clinically useful adjunct to conventional TB diagnostic testing in patients with very low CD4 counts.[38]

For the first time, there might be a point-of-care TB test that works well in people with very advanced AIDS—a group that is difficult to diagnose with sputum smear microscopy, has high mortality from TB, and stands to benefit most from prompt initiation of ART.[39]

Volatile Organic Compound (VOC) Analysis

Volatile organic compounds (VOCs) in breath provide biomarkers of TB because MTB manufactures VOC metabolites detectable in the breath of infected patients.[40]

Gas Chromatography-Mass Spectrometry (GC-MS) Breath Analysis

Kolk et al.[41] investigated the potential of breath analysis by gas chromatography-mass spectrometry (GC-MS) to discriminate between samples collected prospectively from patients with suspected TB. With an accuracy of 79%, the results are similar to those of Phillips et al.[42] and Kolk.[43] GC-MS breath analysis can differentiate between TB and non-TB breath samples even among patients with a negative ZN sputum smear but a positive culture for

MTB. The study concluded that more research into breath analysis is now needed.

BCA 5.0

Phillips et al.[44] evaluated the BCA 5.0 (Menssana Research Inc., United States) in the Philippines, the United Kingdom, and India. The study evaluated breath VOC biomarkers in people with active pulmonary TB. Breath samples are collected and analyzed by gas chromatography for the detection of VOCs. The investigators reported detection of active pulmonary TB with 80% accuracy, 71.2% sensitivity, and 72% specificity. However, 87% of positives were false, which indicates that further refinement of this approach will be necessary before any field use can occur.

Other Diagnostics in the Pipeline

Several other diagnostics may be in the pipeline, but have no published studies. The TrueNAT MTB test by Bigtec labs and Molbio Diagnostics (India) is said to detect TB DNA in sputum within one hour by processing sputum on a semiautomated, battery-operated, portable device.[45] The TrueNAT MTB test and devices are currently under clinical evaluation in two other locations in India and South Africa, and more studies are planned in 2012.

Genedrive is a point-of-need genotyping and sequence-analysis device being made by Epistem (United Kingdom). Epistem's product information states that Genedrive has been designed as a handheld device that analyzes nucleic acids and proteins from fresh or stored biospecimens in clinical settings. Human TB validation studies are under way Spain, India, and South Africa. Epistem expects to be awarded CE/IVD accreditation (European Union accreditation for medical devices) in 2012.[46]

B-SMART (Sequella, Inc., United States) is a test designed to rapidly detect the presence of TB bacteria with resistance to the four front line anti-TB drugs: rifampicin, isoniazid, streptomycin, and ethambutol[47] directly from sputum.[48] Sequella states that the B-SMART prototype assay detects TB bacteria with at least the sensitivity of the sputum smear (<1,000 cells). The developers hope that optimization will significantly increase sensitivity (<50 cells) in order to assess TB drug resistance in smear-negative, culture-positive clinical samples. A study is ongoing.

A project conducted by FIND (Switzerland) and MBio Diagnostics, Inc. (United States) designed to determine a set of serodiagnostic TB antigens for diagnosis

of active disease, which will eventually result in a POC assay format, has progressed to the development of a platform POC test that will enter field evaluation in 2012. FIND and MBio are planning a clinical study at two field sites in developing countries.[49]

While many of the emerging technologies look promising, it remains to be seen if they actually live up to their potential in rigorous clinical and demonstration studies in routine programmatic settings. A recent study by Denkinger et al.[50] showed that optimism bias is a concern with package inserts of TB diagnostics (i.e., industry claims); they compared test accuracy for TB diagnostics reported in 19 package inserts against estimates in published meta-analyses, and found that package inserts generally report overoptimistic accuracy estimates. However, package inserts of most tests approved by the FDA or endorsed by the WHO provide more realistic estimates that agree with meta-analyses.

Global and National Diagnostics Policy Development

Over the past decade, at least 20 new diagnostic test platforms have been discovered, developed, and evaluated.[51]

Many countries will not adopt a test unless it is first recommended by the WHO, which endorses new tuberculosis diagnostics by using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) process. This process is mostly based on test accuracy, with limited cost and feasibility data. The WHO's 2010 *Handbook for Guideline Development* states that a "recommendation is then made which is strong or conditional/optional/weak (for or against an intervention)." The *Handbook* also states that the GRADE process takes into "account the benefits and downsides, values and preferences, impact, and resource use. This is balanced with the quality of evidence (high, moderate, low, very low), the methodological quality of evidence, any likelihood of bias and by outcome and across outcomes."[52]

A new approach to developing policies is now being discussed, and Cobelens et al. have called for a revision of this system to speed adoption of new diagnostics for tuberculosis.[53] The proposed policy process is now envisioned as having two steps: an initial technical recommendation, followed by a programmatic recommendation. Cobelens et al. suggest that the technical recommendation would still follow the current GRADE process and be based on test accuracy with limited costing and feasibility data, however, programmatic recommendation would include patient-important outcomes, cost-effectiveness when implemented under routine conditions, and other factors

critical to successful scale-up at the country level. The evidence for both steps should be systematically collected, but each requires different study designs.[54] The new value chain separates activities at the global level from activities that need to occur at the country level. It also involves multiple feedback loops whereby evidence at each level can inform subsequent decisions to scale up new technologies (or not), and decisions to modify or revise existing policies based on epidemiological impact (or lack thereof) at the country level.

Discussions around when to scale up new diagnostics and how to include them in diagnostic algorithms have increased recently, particularly in light of the rollout of GeneXpert.[55,56] These discussions will ensure that appropriate polices that enable countries to implement rapidly are developed. However, we strongly recommend that the policy development process not allow a country to delay implementation until it has conducted its own field trials for every new test.

Xpert MTB/RIF Progress

A number of countries have been rolling out the Xpert MTB/RIF test following its endorsement by the WHO and the U.S. Federal Tuberculosis Task Force in 2010. GeneXpert is an automated diagnostic molecular testing system, which simultaneously detects TB and rifampicin drug resistance (using Xpert MTB/RIF cartridges) in less than two hours.[57] Widespread implementation of Xpert RIF/MTB began in 2011. According to the WHO and FIND, by March 2012, a total of 611 GeneXpert instruments (comprising 2,979 modules) and 863,790 Xpert MTB/RIF test cartridges had been procured in 61 countries under concessional pricing (WHO GeneXpert Update 2012).[58]

South Africa procured over half of the Xpert MTB/RIF cartridges (478,980); the rest were acquired by other countries as follows: Kenya (34,310); India (25,640); Pakistan (22,440); Zimbabwe (21,570); Tanzania (20,370); Nigeria (18,160); the Philippines (17,440); and Brazil (16,730).[59] At an April 2012 meeting hosted by the Stop TB Partnership Global Laboratory Initiative and the WHO in Annecy, France, Xpert MTB/RIF early implementers noted that the need to reduce the price of the Xpert MTB/RIF test cartridge from US$16.86 to under US$10.00 is a priority, as participants saw cost as a major obstacle to an accelerated and sustainable rollout of the technology in low- and middle-income settings. In order to accelerate implementation, private-sector purchasers in many high-burden countries such as India and South Africa also need to be able to access the concessional prices offered to national TB programs, participants at the meeting said.[60]

Chang et al. reported on a meta-analysis to evaluate the rapid and effective diagnosis of tuberculosis and rifampicin resistance with Xpert MTB/RIF. The meta-analysis included "18 studies covering 10,224 specimens" and found that the accuracy of Xpert MTB/RIF in detecting pulmonary TB and RIF resistance was a "pooled sensitivity of 90.4%, pooled specificity of 98.4%; and for RIF, the pooled sensitivity was 94.1% and pooled specificity, 97%." Xpert performance in detecting extrapulmonary TB was found to be pooled sensitivity of 80% and pooled specificity of 86%.[61]

Xpert MTB/RIF rollout: The South African experience

South Africa has procured over half of all GeneXpert machines and Xpert MTB/RIF cartridges to date. A pilot phase was initiated in National Health Laboratory Services (NHLS) microscopy centers in high-focus TB areas. A progress report on the implementation by the NHLS shows that at least one instrument was placed per province preferentially in districts that had a high burden of TB. The report stated that "twenty-five microscopy centers were selected and a total of 30 instruments placed."

According to the NHLS progress report, as of March 27, 2012, a total of 311,117 specimens had been processed. The total percentage of TB detected in this cohort was between 16% and 17%; the national average was 16.74% (52,068 positive tests). Average rifampicin resistance-detection rates have remained around 7% since the start of the project. A cluster-randomized pragmatic trial within the NHLS rollout of Xpert MTB/RIF will also be conducted in South Africa. It aims to evaluate the impact and cost-effectiveness of routine rollout of Xpert MTB/RIF. The study will also look at the impact on patient and program outcomes, and transmission at a population level. Patient outcomes will be measured for TB suspects and TB patients, and will include six-month mortality amongst TB suspects as the primary outcome. Upon completion of the study, researchers will also be able to determine whether the introduction of Xpert MTB/RIF alters provider behavior with respect to investigating TB suspects, and to estimate costs from the patients' perspective.

Comprehensive economic costs (including costs to the health system) are also being measured, together with the parameters required for the modeling of population impact. For example, a study by Andrews et al. based on modeling shows that Xpert MTB/RIF is cost-effective when using the diagnostic to screen individuals initiating ART. The study results indicate that when compared to no screening, life expectancy in patients with TB disease increased by 1.6 months using smear in symptomatic patients, and by 6.6 months with two Xpert samples in all patients.

Source: Regarding GeneXpert MTB/RIF progress report.[66]

Pediatric TB Diagnostic Update

Accurate diagnosis of TB in children poses multifaceted challenges that current diagnostic tools inadequately address. The childhood TB diagnostic research pipeline has been hampered by technical and clinical difficulties that have only recently been resolved. Chief among these challenges are the difficulty of obtaining sputum specimens from children, the slow growth of the organism in culture, and the diverse and relatively nonspecific clinical presentation of TB in children. Alternative samples for diagnostic testing in children through stool, urine, and saliva are now being explored, but nothing substantial has been advanced. Until recently, there was little consensus in the childhood TB research community on case definitions, as diagnostic classifications and reference standards vary dramatically among researchers.

Recently, the National Institutes of Health (NIH) set out to establish a new reference standard for the diagnosis of TB in children.[67] Leading childhood TB researchers and clinicians agreed on research reference standards and clinical case definitions for intrathoracic TB diagnosis in children. The experts also agreed to try to harmonize methodological approaches for evaluating new diagnosis tools in children.[68]

The consensus case definitions agreed to by the expert meeting are outlined below.

Clinical Diagnostic Groups	Definition of Case Categories
Confirmed tuberculosis	Patients with suspected TB should be classified as "confirmed TB" when: 1. they present with at least one of the signs and symptoms suggestive of TB; and 2. microbiological confirmation is obtained
Probable tuberculosis	Patients suspected of tuberculosis should be classified as "probable tuberculosis" cases when: 1. they present with a least one of the signs and symptoms suggestive of TB; and 2. chest radiography is consistent with intrathoracic disease due to MTB; and 3. there is at least one of the following: a) a positive clinical response to antituberculosis treatment; b) documented exposure to MTB infection; or c) immunologic evidence of MTB infection

Possible tuberculosis	Patients suspected of tuberculosis should be classified as "possible tuberculosis" when they present with at least one of the signs and symptoms suggestive of tuberculosis; and either 1. one of the following: a) a positive clinical response to antituberculosis treatment; b) documented exposure to MTB infection; or c) immunologic evidence of MTB infection or 2. chest radiography is consistent with intrathoracic disease due to MTB NB: if at least one of (1) and (2) are both present, then this case should be classified as "probable tuberculosis"
Tuberculosis unlikely	Symptomatic, but not fitting the above definitions, and no alternative diagnosis established
Not tuberculosis	Fitting the diagnosis for "tuberculosis unlikely," but with an established alternative diagnosis

Source: Evaluation of tuberculosis diagnostics in children.[69]

Now that a pathway for classifying children with TB for diagnostic research purposes has been established, we can hope for better research and more data on new TB diagnostic tests for children in the near future. In a first-of-its-kind prospective study of 452 children under the age of 15 in Cape Town, South Africa, using Xpert MTB/RIF, accuracy exceeding that of microscopy was demonstrated in detecting TB in children.[70]

The study compared Xpert with culture using repeated induced sputum specimens, and findings showed that Xpert detected 76% of culture-proven TB cases, as opposed to 38% of cases detected using microscopy. The study suggests that Xpert is more sensitive than smear microscopy in detecting pulmonary TB in the children. However, almost a quarter of children with culture-confirmed TB were negative on Xpert testing, with an even higher proportion in smear-negative culture-positive children. Sixty-five percent of the children put on TB treatment in the study had both a negative culture and a negative Xpert test. Interestingly, the GeneXpert tool performed more accurate diagnosis of TB in HIV-positive children than on HIV-negative children. However, the study authors found that the number of children with HIV and culture-proven TB was too small to confirm whether sensitivity was indeed increased. Additionally, the study was inconclusive in determining enhanced rifampicin resistance as too few rifampicin-resistant cases were detected. Study authors conclude that culture should not yet be replaced with Xpert, but that it is superior to microscopy for rapid diagnosis, and critical for the detection of MDR-TB.

Another recent study in children evaluating the performance of Xpert in an HIV/TB-endemic setting in southwest Tanzania provided similar data and confirmed accuracy of Xpert in identifying smear-positive and smear-negative culture-confirmed TB cases.[71] While encouraging, these studies are the first of their kind and more evaluation of Xpert in children is needed in varied settings to conclusively prove positive findings.

Recommendations

Point-of-Care Test

Millions of TB cases go undiagnosed each year because of the ineffectiveness, inaccessibility, or expense of current diagnostic technologies. The development of a true dipstick POC test that is rapid and affordable can be used at any location where health care is provided and does not require electricity or specialist training is the ideal TB diagnostic tool that would revolutionize TB control efforts worldwide.

Researchers estimate that if widely implemented, a POC with 100% accuracy could save 625,000 lives per year, and a test with only 85% sensitivity and 97% specificity might save 392,000 lives, or 22.4% of the current annual worldwide deaths attributable to TB.[72,73]

As such, there is an urgent need to accelerate investment to identify biomarkers that can detect those at risk for progression from TB infection to active disease, and biomarkers correlated with disease, cure, and drug resistance. Recognizing this need, several funders such as the Bill & Melinda Gates Foundation and the NIH have recently poured resources into the TB diagnosis biomarker research pipeline and a number of novel—but still nascent—technologies have since been identified. This is a start, but more can and needs to be done. Greater resource mobilization is needed to develop a low-cost and effective POC diagnostic test that can be used in all settings. Public and private sponsors need to collaborate to invest in TB diagnostic development.

Preserve and Modernize TB Sample Banks

Well-characterized specimens from people with and without TB and at various stages of disease and cure will be required to discover, develop, and validate an effective TB point-of-care test.[74] These sample banks need to be operated efficiently and have a clear open-access policy to facilitate the identification and validation of biomarkers.

In 2010, the U.S. Food and Drug Administration provided seed funds for a sample bank called the Consortium for TB Biomarkers (CTB2). CTB2 is hosted by the TB Alliance and works in partnership with the U.S. Centers for Disease Control and Prevention's Tuberculosis Trials Consortium (TBTC) and the AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases (NIAID). Since its inception, CTB2 has gained considerable capacity to collect and process well-characterized samples, which are stored in an international repository and available for researchers who are investigating TB disease, treatment, and cure.

In the spring of 2012, NIAID awarded the consortium an additional five-year grant to support the discovery of new TB biomarkers.[75] Without more reliable TB biomarkers, TB clinical trial patients must be closely monitored for relapse for up to a year following treatment, which greatly increases the length and cost of TB clinical trials. The discovery of TB biomarkers could dramatically revolutionize TB clinical trial research by enabling researchers to more quickly distinguish patients who have been cured and those who are at risk of relapse. A biomarker discovery would go a long way toward enabling the testing of improved drug regimens in a faster, more effective way.

The ongoing support for CTB2 is a positive development; however, the only other sample bank in the world—the WHO's Special Programme for Research and Training in Tropical Diseases (TDR)—is in serious jeopardy of being closed due to budget cuts and lack of prioritization. The TDR specimen bank has an essential role to play in facilitating the discovery and validation of novel biomarkers, as well as in the development of new diagnostic tests. While there remain some institutional challenges with the current setup of the specimen bank—particularly in relation to specimen collection and distribution—these problems can and ought to be fixed. The bank should be expanded rather than closed so that a wider variety of samples—such as those for pediatric TB and non-sputum samples—can be collected to support research required for the development of new diagnostics.

Enhance Uptake of the Xpert MTB/RIF Test by Reducing Machine and Cartridge Prices while Decentralizing the Test's Availability

Despite the unprecedented global interest in and need for the Xpert MTB/RIF test, rollout of the technology has been severely hampered by the extremely high cost of the machines and cartridges. Further, maintenance of the machines when placed on the ground is expensive, complicated, and slow. As of this writing, a market intervention deal has been reached between Cepheid and UNITAID, along with the U.S. government and the Bill & Melinda Gates Foundation, to reduce pricing and expand rollout of the GeneXpert machines.

According to Cepheid, the manufacturer of the device, price reductions were nonnegotiable until a set volume of machines and cartridges were sold; however, since the machines and cartridges were too expensive to buy and maintain, the volume needed to realize the price decrease was never met. In an attempt to break this impasse, UNITAID brokered a multimillion-dollar agreement to scale up access to Xpert via a strategic market intervention. The deal made between UNITAID, the Bill & Melinda Gates Foundation, the U.S. government, and Cepheid in June 2012 included a one-time US$11.1 million buy-down payment that triggered the needed volume, thereby reducing the cost of the cartridges from US$17.00 to US$9.98 each for over 145 public-sector and NGO purchasers in low- and middle-income countries worldwide.

This collaborative market intervention is an important achievement but more still needs to be done to increase access to this revolutionary diagnostic device. Civil-society advocates have called on the manufacturer to further bring down the price of the machines and cartridges to US$7 to enable greater access to the lifesaving diagnostic. Additionally, they have proposed a tiered pricing system that would enable private-sector providers in TB-endemic settings to have access to the system. Advocates have also called for increased transparency on the current manufacturing cost of the machines and cartridges. Finally the scale-up of Xpert in South Africa—where it is being installed in every district, but administered by the NHLS, a quasi-governmental organization separate from the public health services, indicates that there is still too much lag time between test read-out and communication of test results to providers and patients, meaning that appropriate treatment may in some cases be delayed. Thus, further decentralization of Xpert and its integration directly into public health facilities is warranted.

Address Regulatory Gaps in TB Diagnostics

Accessible, inexpensive, and quality-assured TB diagnostics continue to remain elusive in high-TB-burden settings around the world. Additionally, poor regulation of the TB diagnostics market in some TB-endemic areas continues to hamper accurate diagnosis, lengthening the time to effective treatment and cure.

As referenced in last year's pipeline report commercial serological tests for TB antibody detection are being used in at least 17 of 22 high-TB-burden countries, despite evidence of their poor performance, and though no international guideline recommends their use.[76]

Further, it is estimated that 1.5 million serological tests were done every year in India at a conservative cost estimate of US$15 million—most of which

was borne by patients.[77] Further, the TDR conducted an evaluation of the performance of 19 commercially available rapid antibody detection tests for the diagnosis of TB, and found that the sensitivity of all the tests was very low, the highest being 59.7%.[78] As indicated in last year's pipeline report, because of these data, STAG-TB passed a negative recommendation against the use of commercial serological tests for TB in 2010.[79,80,81]

In 2012, FIND and Becton, Dickinson and Company (BD) launched an initiative with the private Indian Kasturba Medical College (KMC) to assist in the promotion of accurate diagnosis of MDR-TB in HIV-positive people in the northern region of Karnataka.[82] The 18-month-long BD/FIND/Kasturba collaboration works by increasing access to BD's BACTEC MGIT system at a lower price and by providing greater access to technical expertise. The collaboration will also enable KMC to become accredited to perform culture- and drug susceptibility testing. These types of innovative public-private collaborations allow access to reliable TB diagnostic equipment and promote initiation of appropriate treatment regimens from onset, thereby reducing the spread of disease.

More still needs to be done—information about WHO-recommended TB diagnostic tests and algorithms needs wider dissemination, particularly to TB providers and civil-society organizations to promote the proper use of good tests and procedures, and to prevent the use of inaccurate diagnostics.[83] Regulation of diagnostics in high-burden countries needs to be improved, and incentives are needed to encourage the private sector to replace serological tests with WHO-endorsed tools.[84]

Conclusion

The future of biomarker-driven assays and technological platforms to diagnose and guide therapeutic development and treatment of TB is very promising—particularly with molecular TB diagnosis and drug susceptibility testing. As TB pathogenesis research efforts improve, we are getting closer to finding a true point of care tool that will accurately diagnose TB. The technical and financial hurdles that need to be overcome to realize the end goal of a rapid, point-of-care test are substantial, but not insurmountable. However, a meaningful commitment to stopping the TB epidemic cannot be met without an increased, sustained research agenda for the development of new diagnostics. The future holds great promise that can only be met by rapidly improving and investing in TB diagnosis technology for the millions of people with TB worldwide.

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THE TUBERCULOSIS TREATMENT PIPELINE

By Erica Lessem

Introduction

Tuberculosis (TB) persists as a global health problem, suffering from both insufficient funding and political will. As a result of poor treatment options and inadequate administration of care, increasingly intractable drug-resistant (DR) strains of the disease are developing.[1,2] Nevertheless, major advances in the fight against TB in the past year inspire optimism.

Implementers, activists, policy makers, and researchers met last month in Cambridge, Massachusetts, to begin discussions about how to reset the global community's target to zero new TB infections, zero TB deaths, and zero TB suffering and stigma.

Founded in fall 2011, the Global TB Community Advisory Board, a group of activists from around the world who are extensively involved in HIV and TB research networks, convened to increase community involvement in tuberculosis research and to mobilize political will regarding key TB product-development issues.

Several community and household-level intervention studies demonstrated the importance of case finding and treatment of latent TB infections, particularly among people with HIV. The World Health Organization (WHO) issued guidelines to integrate TB and HIV service delivery, and many studies are being done to examine the drug-drug interactions (DDIs) between commonly used antiretrovirals (ARVs) and new and existing TB drugs.[3]

The TB Alliance helped revitalize the traditionally slow and inefficient drug-development paradigm by presenting promising results of the first preliminary study of a novel combination treatment regimen, and by initiating the first trial to study both drug-sensitive TB (DS-TB) and multidrug-resistant TB (MDR-TB, or TB that is resistant to at least isoniazid and rifampicin) together, using the same treatment for both.

At the end of 2011, Otsuka filed for European Medicines Agency (EMA) approval for its new drug delamanid (OPC-67683) for treatment of drug-resistant TB—the first new drug and new class of drugs submitted for approval to a stringent regulatory authority in 40 years. Including delamanid, six new drug candidates from four different classes are in mid-stage clinical trials for TB. Finally, on July 2, 2012, Janssen Therapeutics announced its filing a New Drug

Application (NDA) for bedaquiline (TMC207) with the U.S. Food and Drug Administration (FDA) for treatment of drug-resistant TB.[4]

LATENT TB INFECTION

One-third of the world is estimated to have latent TB infection (LTBI), making over 2 billion people potential future TB cases. Treating LTBI is essential to reaching zero new infections from TB. Many recent studies aim to optimize LTBI treatment, either by adding new drugs to shorten treatment duration or by conducting operational research to maximize the benefits of the current standard of care, 6–12 months of daily isoniazid preventive therapy (IPT). Research is also beginning to tackle LTBI in the contacts of DR cases. Options for preventive therapy of DR-TB are essential, especially as a recent study in India found that contacts of isoniazid-resistant TB patients are more likely to be infected than are contacts of isoniazid-susceptible cases (although incidence of TB disease was similar in both groups).[5]

High-burden countries are recognizing the importance of treating LTBI. For example, Botswana's efforts in the past decade to ramp up IPT resulted in the enrollment of 72,000 eligible patients between 2005 and 2007. Mozambique increased the number of HIV patients receiving IPT almost twentyfold from 2008 to 2010. South Africa's ambitious new National Strategic Plan, rolled out in December 2011, has a long-term vision that includes zero TB and HIV infections, and calls for all South Africans to be screened and tested for TB at least once yearly. Many countries, however, still require IPT scale-up. In particular, to conform with the WHO Policy on Collaborative TB/HIV Activities, IPT scale-up for people (especially women and children) coinfected with HIV is necessary.[6]

The TB Trials Consortium (TBTC), an international research network funded by the U.S. Centers for Disease Control and Prevention (CDC), completed PREVENT TB, a study with Sanofi-Aventis to evaluate rifapentine in treatment-shortening regimens for LTBI and active disease. PREVENT TB, or TBTC Study 26, determined that 12 weeks of once-weekly isoniazid and rifapentine under directly observed therapy were as effective as the standard, self-administered nine months of daily isoniazid. Moreover, patients in the 12-week arm had higher completion rates and less liver toxicity.[7] These promising outcomes resulted in a recommendation by the CDC in December 2011 of the 12-week regimen of once-weekly isoniazid and rifapentine under direct observation.[8] Results of substudies including children and people living with HIV show the regimen to be well tolerated in these populations; those results will be published in 2012.[9] Sanofi-Aventis is working on both a fixed-dose combination (FDC) and a dispersible form to facilitate the regimen's administration in various settings and to children.[10]

TABLE 1. Latent Tuberculosis Infection (LTBI) Studies as of June 2012

Study	Regimen	Sponsor(s)	Population and Study Location(s)	Status
A5279	Daily rifapentine + isoniazid for 1 month	ACTG*/ IMPAACT+	HIV-infected population in high-prevalence regions	Enrolling
A5300 (TBTC† Study 35)	To be determined (bedaquiline proposed)	ACTG*/ TBTC†	Close contacts of individuals with multidrug-resistant TB	On hold; drug not available
iAdhere (TBTC† Study 33)	Once-weekly rifapentine + isoniazid for 12 weeks (self-administered)	CDC/ TBTC†/ Sanofi-Aventis	Adults diagnosed with LTBI in the United States, Spain, South Africa, Brazil, and Hong Kong	Pending (enrollment expected to begin mid-2012)
PREVENT TB (TBTC† Study 26)	Once-weekly rifapentine + isoniazid for 12 weeks (directly observed)	TBTC†/ IMPAACT+/ Sanofi-Aventis	Persons with LTBI and high risk of progression (close contacts, recent converters, HIV+, fibrosis on chest X-ray [including children and people with HIV in substudies]) in the United States, Canada, Brazil, and Spain	Main study completed; subgroups of children and HIV+ persons in follow-up
Thibela (CREATE)**	Daily isoniazid for 9 months	CREATE**/ BMGF***	Mine employees and contractors in South Africa	Complete
THRio‡ (CREATE)**	Daily isoniazid for 6 months	CREATE**/ BMGF***	People with HIV attending HIV clinics in Brazil	Complete
ZAMSTAR (CREATE)**	Enhanced case finding and household interventions	CREATE**/ BMGF***	High TB/HIV burden communities in South Africa and Zambia	Complete

*National Institute for Allergy and Infectious Diseases/AIDS Clinical Trials Group
†Centers for Disease Control and Prevention/TB Trials Consortium
**Consortium to Respond Effectively to the AIDS/TB Epidemic
***Bill & Melinda Gates Foundation
+International Maternal Pediatric Adolescent AIDS Clinical Trials Group
‡TB/HIV in Rio

As directly observed therapy is not ideal for all programs and patients, the TBTC is also planning the iAdhere study (Study 33) to evaluate adherence to this new regimen given self-administered versus with directly observed therapy. The study will have two self-administered arms, one with and one without text-message reminders to patients to take their medication.[11] Results of this phase

IV study should help optimize the use of the 12-week isoniazid and rifapentine regimen in TB programs worldwide.

The AIDS Clinical Trials Group (ACTG) and the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT)—two research networks funded by the Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID) of the U.S. National Institutes of Health (NIH)—are building upon the treatment-shortening success of rifapentine and isoniazid with their plans to initiate a one-month regimen of daily rifapentine and isoniazid to treat latent TB in HIV-infected individuals. Study A5279, now enrolling, will contribute to dramatically shortening the time of LTBI treatment if the regimen proves successful.[12]

The ACTG, TBTC, and IMPAACT are also planning ACTG Study A5300 (also known as TBTC Study 35) to examine regimens for preventing TB disease in those 13 years and older who have household contact with persons with confirmed DR-TB. Originally, this study planned to evaluate the efficacy and tolerability of the new compound bedaquiline compared with isoniazid, but bedaquiline's sponsor, Janssen Infectious Diseases, is waiting for additional experience with the drug in patients before making it available for use in LTBI studies. The study design team is now looking to animal-model studies at the Johns Hopkins University to determine the best available drugs to use for DR-TB prophylaxis in place of bedaquiline.[13] A clinical trial for DR-TB prophylaxis would constitute a critical step toward reducing DR-TB incidence.

In addition to these studies of new regimens for treating LTBI, data are also available from three important studies on implementation of IPT and other methods to reduce TB incidence and prevalence. The Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE)—a group of research institutions based in Brazil, South Africa, the United States, and Zambia—led these studies.

The Thibela study, the largest IPT trial ever, examined whether community-wide administration of IPT could affect TB incidence in South African mines, where it is extremely high. This cluster-randomized trial enrolled 27,000 employees and contractors in 15 mine shafts. Those in clusters in the intervention arm received community education and TB screening, and if they did not have active TB, nine months of IPT and monitoring. Workforces in the control arm received the usual TB control program activities at their site. The results of Thibela showed that IPT has a dramatic impact on preventing TB in individuals while they are on therapy; however, the intervention did not durably reduce TB incidence at the community level.[15,16]

Scientific and regulatory challenges in therapeutic clinical trials

Several scientific and regulatory challenges threaten the field of TB clinical research. The endpoints for phase II and phase III studies are controversial and complicated. Follow-up for relapse often requires two years and multiple patient visits. Particularly in the case of MDR-TB and XDR-TB trials, where treatment with optimized background regimens can take years, these lengthy and cumbersome follow-up periods hinder timely drug development. To make research more efficient and enable drugs to move more quickly through the development pipeline, increased research into biomarkers and other predictors of cure and relapse is urgently needed.

Promisingly, based on its use of symptomatic endpoints for clinical trials for the treatment of community-acquired bacterial pneumonia, the U.S. Food and Drug Administration has also expressed openness to considering full approval for TB treatment based on a combined microbiological endpoint (e.g., durable culture conversion) plus a combined symptomatic endpoint, while requiring clinical follow-up for relapse.[14] As all patients in this trial design would contribute data (time to culture conversion, and time to symptom resolution) for the approval endpoint, the pivotal study would not need to be powered to detect statistically significant differences in relapse rate, so long as relapse rates followed the same direction as the clinical and microbiological data. Thus, the acceptance of microbiological and symptomatic endpoints could be a game-changer in TB treatment trials by allowing them to be smaller and less expensive.

Another scientific challenge is the study of close contacts of MDR-TB cases. As MDR-TB is, by definition, resistant to isoniazid—the recommended drug for treating LTBI—IPT would not be effective in this population. However, it is unclear what drug(s) would be effective as standard treatment for LTBI in contacts of MDR-TB cases, particularly as some cases may have resistance to drugs in addition to isoniazid and rifampicin. These scientific challenges are compounded by an understandable reluctance of drug sponsors to administer investigational drugs to healthy patients with LTBI without full evidence of safety from testing in sick trial participants.

The THRio (TB/HIV in Rio) study examined an IPT training and education intervention in 29 HIV clinics in Rio de Janeiro, Brazil, with 18,000 HIV-infected clients. This study compared incidence of active TB and mortality in clinics where patients received the IPT intervention with incidence in clinics where they had not yet received it, with all 29 clinics phased into the intervention by

the study's conclusion. Results indicate that IPT implementation can reduce TB incidence and death in regions with high TB and HIV burdens.[17]

The contrasting results between Thibela and THRio may be attributable to the unique population in the former. Both silicosis (a lung disease caused by inhalation of silica dust) and HIV infection are relatively common among miners in South Africa, and both increase the risk of TB. The Thibela research team was not allowed access to participants' HIV status; however, HIV status was unlikely to be a confounder as the intervention and control clusters were balanced on all other variables (including self-reported HIV status). Additionally, Thibela's results showed that the effect at the individual level of preventing TB is not durable once participants stop taking IPT. Finally, it was challenging to get entire communities at a time on IPT; however, even when 100% uptake was reached and a population-level effect was seen, the effect waned rapidly. Other reasons for lack of effect may be high ongoing rates of TB transmission and vulnerability due to HIV and silicosis. Modeling based on data of participants leaving and reentering their mining community will shed light on whether migration in these communities allows for re-exposure and introduction of TB infection.[18,19,20]

The ZAMSTAR study, one of the largest community-randomized trials, looked at the impact of different interventions on TB prevalence in Zambia and South Africa. Enhanced case-finding interventions, including widespread access to sputum smear microscopy outside of regular health services, did not seem to affect TB prevalence. However, interventions (the evaluation of household contacts of TB patients, with counseling, HIV testing, TB testing, and referral to services) in the homes of patients with TB in high TB/HIV-burden communities did show a nonsignificant trend in reducing the prevalence of culture-positive TB by 22% compared to communities without the intervention. Moreover, children living in the household-intervention communities were half as likely to become infected with TB as their counterparts in the control communities.[21] These results have now been taken up widely by the South African and Zambian health authorities, as well as the 15-country Southern African Development Community (SADC).[22,23] The WHO also advocates for the use of widespread IPT in its policy on collaborative TB/HIV activities.[24]

Maternal TB

TB is estimated to cause 6–15% of all maternal mortality, and is one of the top three overall causes of death among women ages 15–45.[25,26,27] Genital TB causes between 1% and 16% of overall infertility, and results in a low chance of conception even after successful diagnosis and treatment.[28] As a result, it also causes painful stigma and social consequences for women. In addition, recent pregnancy is a demonstrated risk factor in developing active TB in women with HIV.[29,30]

TB in pregnancy affects the mother: complications of TB and the need for prolonged treatment lead to increased maternal morbidity and mortality, according to a recent non-systematic review of the implications of maternal TB on obstetric and perinatal outcomes in South Asia.[31] Maternal TB also jeopardizes existing pregnancy, increasing the likelihood of spontaneous abortion, suboptimal weight gain, preterm labor, and the rare transmission of congenital TB.[32] It also affects the newborn, who has an increased risk of neonatal and perinatal mortality, low birth weight, and contracting postnatal TB.[33,34] These risks increase further when mothers are diagnosed late, have advanced disease, and have incomplete or irregular drug treatment, indicating once more the urgency of early and appropriate TB treatment.[35] Proper care of maternal TB can also help reduce mother-to-child transmission of infections.[36]

The WHO and other leading international health organizations recommend the use of first-line drugs to treat DS-TB in pregnancy and while breastfeeding (although streptomycin should not be used during pregnancy).[37,38] IPT is recommended for pregnant women with LTBI who are at risk of developing active disease.[39] Second-line drugs to treat DR-TB have been shown to produce good outcomes for mothers and their children, although there is a need for increased consideration of pregnant women in drug research.[40]

Because early diagnosis and adequate treatment are crucial for women's health and the health of their children, it is critical to integrate early TB screening, prevention, and treatment into reproductive and other health programs. This is especially important in low-income countries, where an estimated 300,000 pregnant women are triply infected with TB, malaria, and HIV, causing severe complications in their pregnancies.[41] Implementing simple symptom screenings for TB, and prompt treatment for latent and active TB when indicated, at PEPFAR and other program sites preventing mother-to-child HIV transmission, and nutritional programs, can save the lives of many women and children.

ACTIVE TB DISEASE

Like LTBI, active TB disease is curable, yet lengthy treatment duration, high pill burdens, adverse effects, and under-resourced TB programs lead to poor adherence and cure rates. This in turn contributes to the development of DR-TB, whose treatment regimen is more difficult, lengthy, and expensive. Fortunately, researchers are working to improve TB treatment for both DS- and DR-TB by optimizing the use of existing drugs, and by studying novel compounds and combinations.

Repurposing Existing Compounds to Treat Active TB Disease

TABLE 2. Existing Drugs in Late-Stage Clinical Studies for Active TB as of June 2012

Agent/Class	Indication*	Study	Phase	Sponsor	Status
clofazimine riminophenazine	DR-TB	STREAM	Phase III	IUATLD††/ MRC-U.K.‡‡	Enrollment pending
	DS-TB/ DR-TB	NC003	Phase II	TB Alliance	Protocol development
gatifloxacin fluoroquinolone	DS-TB	OFLOTUB	Phase III	WHO/ TDR‡‡‡/IRD†††	Follow-up completed
moxifloxacin fluoroquinolone	DS-TB	REMox TB	Phase III	TB Alliance/ Bayer/ MRC-U.K.‡‡/ University College London/ EDCTP+/ KEMRI***	Follow-up
	DS-TB	RIFAQUIN	Phase III	INTERTB†/ EDCTP+	Follow-up
	DR-TB	STREAM	Phase III	IUATLD††/ MRC-U.K‡‡	Enrollment pending
	DS-TB/ DR-TB	NC001	Phase II	TB Alliance	Completed
	DS-TB/ DR-TB	NC002	Phase II	TB Alliance	Enrolling
	DS-TB	RioMAR	Phase II	CDC/TBTC‡	Enrolling

rifampicin (high-dose) rifamycin	DS-TB	Rifashort	Phase III	INTERTB†/ EDCTP+	Planning
	DS-TB	HIGHRIF	Phase II	EDCTP+	Enrolling
	DS-TB	HIRIF	Phase II	NIAID+++	Planning
	DS-TB	RIFATOX	Phase II	INTERTB†/ EDCTP+	Enrolling
	DS-TB	Safety, tolerability, extended EBA, and PK of higher doses of rifampicin in adults with pulmonary TB	Phase II	EDCTP+	Enrolling
rifapentine rifamycin	DS-TB	RIFAQUIN	Phase III	INTERTB†/ EDCTP+	Follow-up
	DS-TB	Randomized open-label trial of daily rifapentine 450 mg or 600 mg in place of rifampicin 600 mg for intensive-phase treatment of smear-positive pulmonary TB	Phase II	FDA++	Enrolling
	DS-TB	RioMAR	Phase II	CDC/TBTC‡	Enrolling
	DS-TB	TBTC Study 29x	Phase II	CDC/TBTC‡/ Sanofi-Aventis	Enrolling
linezolid oxazolidinone	DR-TB	linezolid to treat XDR-TB**	Phase II	NIAID+++	Follow-up

‡‡British Medical Research Council
‡Centers for Disease Control and Prevention/TB Trials Consortium
*DR-TB indicates drug-resistant TB; DS-TB indicates drug-sensitive TB
**extensively drug-resistant TB
+European and Developing Countries Clinical Trials Partnership
†††French Institut de Recherche pour le Développement
†International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis
††International Union Against Tuberculosis and Lung Disease
***Kenya Medical Research Institute
+++National Institute of Allergy and Infectious Diseases
++U.S. Food and Drug Administration
‡‡‡World Health Organization-based Special Programme for Research and Training in Tropical Diseases

Clofazimine

Clofazimine, a riminophenazine derivative approved for the treatment of leprosy, has long been recognized for its bactericidal activity against *M. tuberculosis* in mice.[42] Its inclusion in a reportedly successful nine-month standardized treatment regimen for MDR-TB, and presumed low levels of existing resistance, have contributed to increased recent interest in the drug's potential for development as an antituberculosis agent.[43] However, its common side effect of skin discoloration (and very rare effect of accompanying depression, with two related suicides reported) and possible QT prolongation (which can lead to dangerously irregular heart rhythms) may hinder its ultimate suitability for TB treatment.[44] The results of the STREAM study and the novel combination study NC003 described later in this chapter will further illuminate the safety and efficacy of including clofazimine in new regimens to fight TB.

The International Union Against Tuberculosis and Lung Disease (IUATLD) is sponsoring the Evaluation of a Standardised Treatment Regimen of Anti-Tuberculosis Drugs for Patients with MDR-TB (STREAM) trial, funded by the U.S. Agency for International Development (USAID). It will assess a nine-month standardized treatment regimen for MDR-TB that achieved promising outcomes with a cure rate of 87.9% in a nonrandomized observational study in Bangladesh.[45] Modified after the Bangladesh regimen, which used clofazimine, ethambutol, gatifloxacin, and pyrazinamide for nine months, supplemented by prothionamide, kanamycin, and high-dose isoniazid during an intensive phase of four months, the STREAM regimen uses the same drugs, but substitutes moxifloxacin for gatifloxacin. The aim of this study is to show that this shorter treatment regimen is at least as effective as the current lengthier treatments used throughout the world to treat MDR-TB. The Clinical Trials Unit of the British MRC is conducting this trial and is expected to begin enrollment in several sites in mid-2012.[46]

Fluoroquinolones

Gatifloxacin is a fluoroquinolone, a class of broad-spectrum antibiotics. The OFLOTUB consortium's trial replacing ethambutol with gatifloxacin aims to evaluate gatifloxacin's potential to shorten first-line treatment to four months. The WHO-based Special Programme for Research and Training in Tropical Diseases (TDR) sponsors the OFLOTUB trial with the French Institut de Recherche pour le Développement (IRD). OFLOTUB completed the two-year posttreatment patient follow-up in April 2011, but problems in data management caused unexpected delays in data analysis. Recent progress with the database has addressed these problems, and safety and efficacy results should now be available by the end of 2012.[47]

Like gatifloxacin, moxifloxacin is a fluoroquinolone with treatment-shortening potential. The widespread use of fluoroquinolones may make existing resistance to moxifloxacin problematic; however, a recent case report exemplified the possibility of treating MDR-TB with additional resistance to fluoroquinolones (and pyrazinamide) using high-dose moxifloxacin.[48]

REMox TB is a phase III clinical trial comparing two four-month moxifloxacin-containing treatment regimens (two months of moxifloxacin/isoniazid/rifampicin/pyrazinamide plus two months of moxifloxacin/ isoniazid/rifampicin; and two months of ethambutol/moxifloxacin/rifampicin/pyrazinamide plus two months of moxifloxacin/rifampicin) for DS-TB with the standard six-month TB regimen (ethambutol/isoniazid/rifampicin/pirazinamide). REMox TB is a collaborative effort among the TB Alliance, Bayer HealthCare, University College London, University of St Andrews, the British Medical Research Council (MRC), the European and Developing Countries Clinical Trials Partnership (EDCTP), and the Kenya Medical Research Institute (KEMRI). Initiated in 2008, REMox TB has built strong community-engagement programs at several of its sites, and has helped pave the way for leveraging additional resources for TB research by its use of existing ACTG clinical trial sites.

In February 2012, the TB Alliance announced the completion of enrollment for REMox TB, after over 1,900 patients were enrolled at sites in Africa, Asia, and Latin America. The study will evaluate participants for one year following the completion of their treatment (late 2013). If data analysis shows successful trial results, TB Alliance and Bayer will seek to register moxifloxacin as part of a DS-TB treatment regimen. If approved, registration of moxifloxacin is expected in 2014.[49]

The TBTC-funded, Johns Hopkins-led RioMAR study in Brazil is also examining the role of replacing ethambutol with moxifloxacin, as well as rifamycin with rifapentine, during the intensive phase of treatment.[50] Moxifloxacin is also included in the above-described STREAM study, and in the NC001 and NC002 new combination studies described at the end of this chapter. The upcoming results of the above-described RIFAQUIN study, a pending early bactericidal activity (EBA) study by the ACTG (Study 5307) of TB regimens with and without isoniazid and moxifloxacin (isoniazid for 2 days only versus isoniazid for 2 days and moxifloxacin for 12 days, both with rifampicin/pyrazinamide/ethambutol; versus 14 days of isoniazid/rifampicin/ethambutol/pyrazinamide), should also help clarify the potential of moxifloxacin in TB treatment.[51]

Linezolid

The U.S. National Institute of Allergy and Infectious Diseases (NIAID) sponsored a phase IIa study in South Korea, testing the side effects and effectiveness of prolonged treatment with linezolid at two different doses (in addition to other background therapy). Forty HIV-negative patients with pulmonary extensively drug-resistant TB (XDR-TB, or TB that is resistant to at least isoniazid, rifampicin, a fluoroquinolone and an injectable second-line drug) were enrolled at the National Medical Center in Seoul and the National Masan TB Hospital. Results have been submitted for publication and should be available in 2012.[52]

Rifamycins

Rifapentine, rifampicin, and rifabutin are drugs in the sterilizing drug class of rifamycins, meaning that they have excellent potential to kill all *M. tuberculosis* organisms present in an infection (as long as those organisms are susceptible to rifamycins).

Rifampicin is the most commonly used rifamycin in TB treatment; rifapentine and rifabutin both have longer half-lives. TBTC Study 29x, a safety study substituting rifampicin with 10, 15, and 20 mg/kg daily doses of rifapentine in the standard-of-care regimen, expects to complete enrollment by the end of the year and publish results in 2013.[53] Two open-label trials of rifapentine are also in phase II; the first, the previously described RioMAR study, which also substitutes moxifloxacin for ethambutol, is sponsored by TBTC.[54] The second is funded by the U.S. Food and Drug Administration (FDA) and conducted by the University of Cape Town Lung Institute in collaboration with the Johns Hopkins University, and is anticipated to produce results by May 2013.[55] RIFAQUIN—a phase III study being conducted by the International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB) at St George's, University of London, with funding from the EDCTP—is assessing whether high-dose rifapentine and moxifloxacin, when given together, can shorten first-line treatment, allow for intermittent dosing, and replace isoniazid. RIFAQUIN's treatment phase was completed in July 2011; patients are in follow-up, and results are expected in early 2013.[56] Sanofi-Aventis is initiating a DDI study between rifapentine and ATRIPLA (a combination of the antiretrovirals efavirenz, emtricitabine, and tenofovir disoproxil fumarate) in participants with HIV who have CD4 counts greater than 400 and do not have TB; results are expected by early 2013.[57,58]

The RIFATOX study, which examines the toxicity of 900 mg and 1200 mg daily doses of rifampicin for four months, has reached two-thirds of its target enrollment and expects results in early 2013.[59] Based on these results, a phase

III study called Rifashort will look at the treatment-shortening potential of high-dose rifampicin.[60] The HIRIF study (in planning stages for initiation in late 2012), and two currently enrolling EDCTP-funded phase II studies, will help assess the pharmacokinetics and maximum tolerated dose of higher doses of rifampicin.[61,62,63] The ACTG is planning study A5290 to compare rifampicin- versus rifabutin-based TB treatment for patients with HIV.[64] Médecins Sans Frontières (MSF)/Epicentre is also planning RIFAVIRENZ, a DDI study between high-dose rifampicin and efavirenz.[65]

TB and injection drug use

Injection drug use is associated with many factors that place individuals at high risk for TB, including poor nutritional status, a weakened immune system, HIV and other infections, and substandard living conditions. Given the illicit nature of injection drug use in most settings, people who use injection drugs are often marginalized and have trouble accessing care. Separate silos of services for drug use, HIV, and TB make referrals to care unlikely; even worse, many drug users are imprisoned without medical services.[66] Studies in both high- and low-TB burden settings—such as Denmark, Kenya, Thailand, the United States, and Vietnam—have documented that injection drug use is associated with TB infection, disease, and death.[67,68,69,70]

Operational and programmatic interventions can have a large impact on reducing TB among people who inject drugs. A recent study conducted by the Muhimbili National Hospital in Tanzania and Yale University will present its results shortly, demonstrating that active TB case finding is needed for people who inject drugs in Tanzania, to shorten the time to diagnosis, to improve individual care, and to reduce transmission of TB.[71] The Open Society Foundations' International Harm Reduction Development program is also working to address barriers to care for people with TB who inject drugs, who face particularly harsh stigma in parts of the former Soviet Union.

In addition to programmatic improvements in access to existing diagnostic and treatment options, there is still a great need for more biomedical research to improve TB care for people who inject drugs or are on opioid substitution therapy. Rifampicin, one of the four pillars of first-line therapy for TB, reduces plasma levels of buprenorphine—a drug commonly used to treat heroin- and other opioid dependence—and induces withdrawal symptoms.[72] Rifabutin, another rifamycin, also decreases buprenorphine plasma concentrations, although it does not appear to induce withdrawal; however, rifabutin is not as commonly used as rifampicin in treating TB.[73] Further studies to optimize the dosing of buprenorphine when coadministered with rifampicin, and to examine the interactions between buprenorphine and rifapentine (another rifamycin), are needed to inform integrated TB treatment and opioid dependence services.

Novel Compounds to Treat Active TB Disease

TABLE 3. Novel and Second-Generation Compounds in Late-Stage Clinical Studies for Active TB as of June 2012

Agent	Class	Sponsor	Status	Indication†	New Combination Study
delamanid (OPC-67683)	nitroimidazole*	Otsuka	Phase III	DR-TB	—
AZD5847	oxazolidinone	AstraZeneca	Phase IIa	TBA	—
sutezolid (PNU-100480)	oxazolidinone	Pfizer	Phase IIa	DR-TB	—
bedaquiline (TMC207)	diarylquinoline*	TB Alliance/ Janssen	Phase II	DS-TB	NC001, NC003
		Janssen	Phase II	DR-TB	
PA-824	nitroimidazole*	TB Alliance	Phase II	DS-TB/ DR-TB	NC001, NC002, NC003
SQ109	diamine	Sequella/ PanACEA‡	Phase II	DS-TB/ DR-TB	—

*indicates new drug class
†DS-TB indicates drug-sensitive TB; DR-TB indicates drug-resistant TB; TBA indicates to be announced
‡The Pan-African Consortium for Evaluating Anti-tuberculosis agents

AZD5847

AZD5847 is an oxazolidinone in development by AstraZeneca for the treatment of pulmonary tuberculosis. AstraZeneca's development of AZD5847 helped make it the third-largest private funder of TB R&D in 2011.[74] Oral AZD5847 has been investigated in two phase I studies—a single ascending dose, and a multiple ascending dose where the drug was administered up to 1,200 mg twice a day for a period of 14 consecutive days. In the former, the pharmacokinetics of AZD5847 were also compared when administered fasting versus fed: administration with food significantly increased its bioavailability and improved gastrointestinal tolerability.

Generally, the compound was well tolerated, and no major safety concerns were identified in either study. There were no clinically relevant treatment-related changes or trends in any laboratory variables, vital signs, or electrocardiograms. In the multiple ascending-dose study, the most common adverse effects were nonserious gastrointestinal disorders; reversible and dose-related changes in white blood cells; and mildly increased reticulocyte

counts at follow-up. Changes in reticulocyte counts were not accompanied by changes in hemoglobin or hematocrit measurements.[75,76,77] A phase IIa study is proposed to begin in the fall of 2012 in patients with DS pulmonary tuberculosis. AstraZeneca has not yet determined if the compound will ultimately be developed for DS-TB or DR-TB.[78]

Bedaquiline (TMC207)

Bedaquiline (also known as TMC207) is the first compound from a new class of drugs called diarylquinolines. Bedaquiline is being developed for DR-TB by Janssen Infectious Diseases BVBA (a subsidiary of Johnson & Johnson formerly known as Tibotec), and for DS-TB by Janssen and the TB Alliance. As noted above, in early July 2012, Janssen filed its NDA with the U.S. FDA for accelerated approval of bedaquline for treatment of DR-TB.[4]

In late 2011, Janssen presented 24-week data from an open-label trial of bedaquiline in adults with smear-positive, confirmed MDR-TB or XDR-TB, including patients with HIV. The data indicated that adding bedaquiline to an individualized MDR-TB regimen was safe and well tolerated and resulted in an overall 81% culture conversion rate at week 24, with median times to culture conversion of 8 weeks for patients with MDR-TB, 12 weeks for patients with pre-XDR-TB, and 24 weeks for patients with XDR-TB. Responder rates were higher for patients with no cavitations (holes in the lungs caused by extensive cell death), patients with a lower extent of resistance, and patients on three or more potentially active drugs in their background regimen. Patients in the trial are being followed while they complete their background regimen.[79]

A recent publication of the two-year follow-up results for a randomized study of 47 patients with pulmonary MDR-TB treated with either bedaquiline or placebo added to the first eight weeks of a background regimen showed that bedaquiline significantly reduced the time to culture conversion over 24 weeks, and was comparable to placebo in terms of adverse events (with the exception of nausea, which bedaquiline caused in more patients). Additionally, though the numbers were small, only one patient receiving bedaquiline acquired resistance to companion drugs (excluding ethambutol and ethionamide) versus five patients receiving placebo.[80] Though the number of study participants involved was small, and the difference in acquired resistance not significant, there is now evidence that the addition of bedaquiline to current MDR-TB regimens may have the potential to reduce resistance.

Janssen now plans to start a phase III trial of 600 subjects with sputum smear–positive pulmonary MDR- or pre-XDR-TB (confirmed by rapid diagnostic test). Participants in the first arm will receive 9 months of bedaquiline and a

background regimen. Those in the control arm will receive placebo and the background regimen. Participants in a third rollover arm, which will capture the failures from the first two arms, will receive an individualized salvage regimen. The primary endpoint will be relapse-free cure at 15 months for those in the first two arms. The final analysis will look at relapse-free cure at 21 months.[81]

Janssen is also taking into consideration TB/HIV-coinfection and pediatric DR-TB in its development plans. The pediatric investigational plan that will guide future clinical studies of bedaquiline in children to establish safe and effective dosing based on age and development has been approved by the EMA and has been shared with the FDA.[82]

The IMPAACT network is currently finalizing the protocol for Study 1108, a pharmacokinetic and safety study of bedaquiline in children with MDR-TB. This study of different age cohorts will begin by placing the oldest children (12–18 years) on an adult formulation of bedaquiline. All younger cohorts (6–12 years, 2–6 years, 6 months–2 years, 0–6 months) will be placed on a pediatric formulation currently in development by Janssen, sequentially from oldest to youngest, once adequate data from the preceding cohort are available. Enrollment is anticipated to start in the first quarter of 2013. The study plans to first enroll HIV-uninfected children in each age cohort, then enroll similar numbers of HIV-infected children, all with proven or presumed MDR-TB. This study is an excellent example of an appropriate pediatric study design that also takes into account TB/HIV coinfection, and of a public-private partnership.[83]

Janssen is conducting DDI studies with ARVs known to inhibit cytochrome P450, a group of enzymes that metabolize bedaquiline. Coadministration with the boosted protease inhibitor lopinavir/ritonavir increased exposure to bedaquiline by approximately 20%, and a trial with nevirapine (NVP) indicated that steady-state NVP did not influence exposure to bedaquiline or its metabolite, and single-dose bedaquiline did not influence pre-dose NVP concentrations.[84] An ACTG-led DDI study of bedaquiline and efavirenz (EVF) similarly showed that single-dose bedaquiline was well tolerated alone and with steady-state EFV, and that changes in bedaquiline concentrations when given with EFV are unlikely to be clinically significant. The DDI results with repeated dosing of bedaquiline have not yet been studied. Further data will be presented by the ACTG at the International Workshop on Clinical Pharmacology of Tuberculosis Drugs in September 2012.

The NIAID Division of Microbiology and Infectious Diseases (DMID) has just completed enrollment of a phase I study examining drug-drug interactions between bedaquiline and rifampin and rifabutin. Final results of this study will be available in late 2012.[85]

Delamanid (OPC-67683)

Delamanid, a nitroimidazole formerly known as OPC-67683, is a novel compound being studied for the treatment of MDR-TB. Delamanid is in a new class of compounds that inhibit mycolic-acid biosynthesis with specificity to mycobacteria, especially *M. tuberculosis*.[86] The specificity of nitroimidazoles' action to the TB bacterium prevents their use for other indications, meaning that widespread resistance generated outside of TB control programs would be unlikely.

Otsuka just published the results of a phase IIb study of two different doses of delamanid plus optimized background regimen (OBR) versus placebo plus OBR in 481 volunteers with confirmed MDR-TB. Of patients receiving 100 mg or 200 mg of delamanid plus OBR, 45.4% and 41.9%, respectively, had sputum culture conversion at two months, as compared with 29.6% of patients receiving OBR and placebo. QT prolongation was more common among those receiving delamanid, although no clinical events due to QT prolongation were observed, and in general, most adverse events were mild to moderate and were distributed evenly across study arms.[87] Thus, delamanid appears efficacious and safe for use as part of an MDR-TB regimen.

As part of the phase IIb trial, a long-term, open-label surveillance of patients with MDR-TB who have been treated with delamanid and OBR is also under way to extend the efficacy and safety observations from the trial, and to further document the durability of response. The results of these studies, and of DDI studies with ARVs, will be published soon in a peer-reviewed journal.[88]

Otsuka recently initiated an international phase III clinical study with delamanid. The randomized controlled trial includes six months of treatment with delamanid as part of a full course of treatment with OBR, and includes HIV-coinfected MDR-TB patients.[89]

Otsuka filed in early 2012 for European Medicines Agency (EMA) approval for delamanid for treatment of DR-TB; a decision is anticipated by the end of 2012. This makes delamanid the first new anti-TB drug, and nitroimidazoles the first new class of anti-TB drugs, submitted for approval by a stringent regulatory authority in the past four decades. Otsuka's investments to develop delamanid make it the leading funder of TB drug R&D, and the leading private-sector funder of TB R&D overall.[90]

PA-824

PA-824, like delamanid, is from a new drug class, the nitroimidazoles. In phase II development by the TB Alliance, PA-824 recently was shown to be safe, well tolerated, and efficacious at doses of 100–200 mg daily in a dose-ranging study among drug-sensitive, sputum smear–positive, adult pulmonary TB patients.

Pediatric TB

Children have long been neglected in the fight against TB, despite making up 15–20% of the global tuberculosis burden.[91] Difficulties in diagnosing TB in children, and the notion that children do not transmit TB, have contributed to this neglect. In particular, few children with DR-TB receive appropriate diagnosis and treatment, despite evidence that even children with MDR-TB can be treated successfully.[92,93] Fortunately, increased attention to fighting pediatric TB is building.

The general principles of treating adults and children are the same.[94] However, children and adults metabolize drugs differently; therefore, doses for children cannot be determined simply by scaling down the adult dose per kilogram.[95] The 2010 WHO guidelines accounted for these differences and updated the recommended dosages of isoniazid, ethambutol, pyrazinamide, and rifampicin. However, the pediatric formulations available on the market today are not tailored to deliver the new dosages, and complex interim dosing guidelines using the current unsuitable fixed-dose combination (FDC) have hindered the implementation of these new recommendations. Treatment providers including MSF have been lobbying the WHO to release recommendations for the composition of a new FDC for pediatric first-line TB treatment that corresponds with these new dosing guidelines. Once the new FDC formulations are on the WHO prequalification expression-of-interest list for drug manufacturers, there will be a need to engage manufacturers to start developing these formulations as quickly as possible. This will facilitate the appropriate and prompt dosing and treatment of DS-TB in children.

To help address the issue of dosing in children, Lucane Pharma recently developed a child-friendly dosing spoon. This tool is validated for the MDR-TB product Paser (p-aminosalicylic acid), a gastroresistant (meaning it is absorbed in the duodenum rather than the stomach, where it could cause damage) second-line drug whose conventional packaging consists of granules in a sachet. The dosing spoon helps care providers measure smaller doses of PAS accurately. As of February 2012, the spoon is being used in Uzbekistan and Tajikistan by MSF, as well as in South Africa by the Desmond Tutu TB Centre in Stellenbosch, and in France. Lucane is working on a similar preparation for isoniazid, and is open to developing similar pediatric-friendly formulations and dosing tools for other drugs useful in the treatment of childhood DS- and DR-TB.[96]

Pediatric DR-TB is also beginning to receive other much-needed attention, thanks in part to the efforts of the Sentinel Project on Pediatric Drug-Resistant Tuberculosis, a group of experts and stakeholders in childhood DR-TB.[97] To facilitate both research and the clinical management of pediatric DR-TB, the group has established standardized definitions for measures of exposure, resistance, site and severity of disease, adverse events, and treatment outcomes.[98] The group is simultaneously publishing a handbook to serve as a practical management tool for pediatric DR-TB to help guide practitioners in the field.[99] Both the definitions and the handbook should be published shortly.[100,101]

The TB Alliance will evaluate PA-824 as a component of novel anti-TB regimens for both DS-TB and DR-TB moving forward.[102] These PA-824-containing novel regimens are being tested in the combination studies described further in the next section of this chapter.

The NIAID DMID and the TB Alliance are cosponsoring a phase I thorough QT (TQT) study to evaluate any effects PA-824 will have on cardiac conduction (the rate at which the heart conducts electrical impulses). The clinical trial will also study whether PA-824 and moxifloxacin had additive or synergistic effects on the QT interval. This study will start enrolling in Q4 2012.[103]

The ACTG has opened a phase I safety, tolerability, and pharmacokinetic interaction study of PA-824 and two common antiretrovirals (ARVs).[104] This study, also called A5306, will look at whether PA-824 is safe to use with lopinavir/ritonavir (a boosted protease inhibitor) and efavirenz (a non-nucleoside reverse transcriptase inhibitor) as well as with rifampicin.[105,106] Given the prevalence of TB/HIV coinfection, these DDI studies between new potential anti-TB agents and commonly used ARVs are essential.

In late 2012, the TB Alliance plans to file an investigational new drug (IND) application with the FDA, and to start a phase I program for its backup nitroimidazole, the new drug candidate TBA354, which is currently in preclinical development.[107]

SQ109

SQ109, a second-generation ethylene diamine antibiotic, is the lead compound from Sequella. In a phase IIa early bactericidal study, with collaborators from the Pan African Consortium for Evaluating Antituberculosis Agents (PanACEA), Sequella was found to be safe and well tolerated and will be evaluated in a multiple-arm, multiple-stage, phase II study in DS-TB expected to start in 2012. Additional studies in DS- and DR-TB are planned for late 2012/early 2013 with the ACTG. In parallel, Sequella and the Maxwell Biotech Venture Fund plan a late-2012 phase III study of SQ109 for DR-TB in Russia, Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Tajikistan, Uzbekistan, and possibly Turkmenistan and Ukraine.[108]

Sutezolid (PNU-100480)

Sutezolid, or PNU-100480, is a new oxazolidinone—the same class of drugs as linezolid. Sutezolid appears to have more potent antituberculosis activity in vitro, in ex vivo whole blood cultures, and in a murine (mouse) model.[109,110,111,112,113] A whole-blood study also predicted that sutezolid and two drugs described above—SQ109 and bedaquiline—would be additive, and

deserve testing as part of a novel regimen.[114] Pfizer recently completed a phase IIa, open-label, early bactericidal activity and whole-blood activity study. This study of adults with pulmonary DS-TB compared two experimental arms—one with sutezolid twice daily at 600 mg, the other with sutezolid once daily at 1,200 mg—with Rifafour. Results should be available soon.[115]

HIV/TB integration

The WHO's recently updated policy on collaborative TB/HIV activities highlights important steps to integrating TB and HIV service delivery, including increasing case finding; initiating IPT and antiretroviral therapy in individuals with HIV; providing HIV testing and prevention interventions for patients with TB; and ensuring TB infection control in health care facilities.[116] On the research side, DDI studies between commonly used ARVs and TB drugs (both existing and new) are necessary to ensure that coadministration is safe.

In most cases, clearly, it is essential to initiate antiretroviral therapy (ART) as soon as is practicable after starting TB treatment in persons coinfected with HIV; the one exception appears to be in cases of tuberculous meningitis. The Cambodian Early versus Late Introduction of Antiretroviral Drugs (CAMELIA) study showed that initiating ART two weeks versus eight weeks after initiating TB treatment significantly improved survival among HIV-infected adults with CD4 counts below 200 (it is important to note that the average baseline CD4 cell count for this trial was 25).[117] Two other simultaneously published randomized trials, ACTG Study 5221 (START) and the Starting Antiretroviral Therapy at Three Points in Tuberculosis (SAPIT) study showed that earlier ART initiation (within two to four weeks of beginning TB treatment) in people with HIV and CD4 counts below 50 increased survival, but that in individuals with higher CD4 counts, deferral of ART initiation to the continuation phase of TB therapy (two to three months after initiation) may reduce the risk of immune reconstitution inflammatory syndrome and other adverse events without increasing the risk of AIDS or death.[118,119] The average baseline CD4 cell count was 77 for START, and 150 for SAPIT. These study participants clearly did not have HIV disease as advanced as did those in the CAMELIA trial, which may explain the apparent difference in results. A planned meta-analysis of these three trials should help better define criteria and timing for initiation of ART after starting TB treatment.[120]

However, in a randomized, double-blind, placebo-controlled trial of immediate ART versus deferred ART (study entry or two months later) in patients with HIV-associated tuberculous meningitis (who are excluded from the usual TB treatment trials because they need special care due to central nervous system inflammation and higher rates of morbidity and mortality), no difference was found in mortality or the time to new AIDS events or death. Grade 4 adverse events occurred significantly more frequently in the immediate-ART arm. These results support delayed initiation of ART in HIV-associated tuberculous meningitis.[121]

ACTG study A5274, the REMEMBER Study, should shed light on a different aspect of the "when to start" issue by looking at whether full four-drug treatment for active TB should be started only after active TB infection is found, or whether people with HIV and CD4 counts below 50 do better on "empiric" four-drug TB treatment even if they have not been diagnosed with active TB.[122] A similar study called PROMPT is being conducted in Africa with funding from the EDCPT.[123]

Novel Combinations to Treat Active TB Disease

TB treatment requires the delivery of multiple drugs in combination so as to prevent the development of resistance. The traditional drug development paradigm involves substituting a drug in the standard-of-care regimen with one novel compound at a time. In this traditional paradigm, producing a novel regimen can take at least 20 years (the British MRC took 38 years to move from streptomycin monotherapy in 1948 to the standard of care of two months of isoniaizid/rifampicin/pyrazinamide/ethambutol [HRZE] followed by four months of isoniazid/rifampicin in 1986).[124] While early research on individual new drugs is critical to determining safety profiles, efficacy, and dosing, late-stage studies combining multiple novel compounds have the potential to rapidly catalyze regimen change and provide the millions of people with TB access to better care.

To encourage this paradigm shift and shorten the TB drug development timeline, the Critical Path to TB Drug Regimens (CPTR) initiative was founded in 2010 by the Bill & Melinda Gates Foundation, the Critical Path Institute, and the TB Alliance.[125] The FDA has also been instrumental, issuing a guidance in 2010 to facilitate combination studies, awarding support for clinical trials, and in 2012 proposing to lower the risk classification of nucleic acid–based tests for TB to encourage the development of new rapid diagnostic tests for TB. The TB Alliance has made progress on three early-stage (two-week EBA and two-month sputum serial colony count [SSCC]) combination trials, as described below.[126] These combination trials represent a new, potentially unified pathway for DS- and DR-TB drug development, in which drugs in combination are indicated for the treatment of tuberculosis caused by strains sensitive to each drug.[127] That is, patients are treated with drugs to which their organism is sensitive, rather than with combinations against which it is thought they are not resistant; however, this development will require drug-susceptibility testing that takes less than one day—something that now exists only for isoniazid, rifampicin, fluouroquinolones, and injectables).[128]

NC001

The TB Alliance recently completed NC001, the first TB clinical trial to evaluate multiple unapproved new TB drug candidates in combination. This two-week, phase II EBA study tested the three-drug regimen PA-824, moxifloxacin, and pyrazinamide (PaMZ). The PaMZ regimen performed significantly better than the standard of care (HRZE).

The study also tested additional two-drug combinations of PA-824, moxifloxacin, and pyrazinamide and bedaquiline to evaluate their potential as "building blocks" of future regimens. Validating what had been seen in mouse models, pyrazinamide and bedaquiline were synergistic, pyrazinamide and PA-824 had an additive effect, and PA-824 and bedaquiline did not have an additive effect.

The study was also important for helping open up a promising new regulatory pathway for new combination trials. In addition, it demonstrated that EBA studies can distinguish between treatments, not just between doses of the same treatment. NC001 also showed that measuring colony-forming units (which involves comparing the number of remaining viable bacterial cells that can grow into colonies after the experimental and control treatment) and time to positivity (TTP, which measures how long a cultured sputum sample takes to read as positive after therapy, with more effective treatment leaving fewer live bacterial cells and therefore having a longer TTP) gave similar results, helping to validate TTP as a biomarker for treatment response.[129,130]

NC002

Based on the results of NC001, the TB Alliance is evaluating PaMZ for both DS- and DR-TB in NC002, a two-month serial sputum-colony-counting (SSCC) study; SSCC measures the fall in the number of viable counts of *M. tuberculosis* in samples collected under standardized conditions on multiple occasions before and after initiating therapy.[131] The study is slated to take place at eight sites in South Africa, Tanzania, and Brazil, and will advance global capacity for TB trials along with the new innovative approach to TB drug development.[132] This study started enrolling patients in the first quarter of 2012, with results expected in the summer of 2013.[133]

NC003

The TB Alliance is also planning study NC003, which will evaluate the EBA, safety, tolerability, and pharmacokinetics of two weeks of once-daily oral dosing of clofazimine alone, pyrazinamide alone, and various combinations of these drugs with PA-824 and bedaquiline, in comparison with standard first-line TB treatment. NC003 will enroll 105 newly diagnosed adults with smear-positive, drug-sensitive pulmonary tuberculosis. The study is expected to begin enrolling patients in late 2012, with results expected in the summer of 2013.[134]

Preapproval access to compounds

People with XDR-TB and pre-XDR-TB have drastically limited treatment options. Those that exist are effective for only some patients and have major toxicity issues. Moreover, they are often unavailable in communities where they are needed. People with XDR-TB and pre-XDR-TB can't afford to wait the several years it will take for new compounds in development to become approved and available.

The compassionate use of these compounds could potentially provide a lifesaving option to patients otherwise without hope. Compassionate use refers to preapproval provision of compounds to patients meeting strict criteria specified by the local government and the drug sponsor. Expanded access, meaning the extension of a clinical trial to select patients in need who would not normally meet study inclusion criteria, is also an option where compassionate use is not permitted. In both pre- and postapproval instances, new drugs must be used cautiously and in combination with other effective background therapy; this will ensure that further resistance does not develop, and preserve the new compound as an effective treatment option for as many MDR-TB patients as possible.

Based on its HIV experience, Janssen has taken laudable steps to provide the compassionate use of bedaquiline in Europe, the Americas, Africa, and Asia.[135] Otsuka is in the process of developing approaches and models of compassionate use and expanded access for delamanid.[136] The TB Alliance is also proposing a collaborative investigational "rescue" study of a combination of at least three new drugs in development from novel classes (meaning they will not face preexisting resistance) in patients with XDR-TB. Potential collaborators include Otsuka, Janssen, Pfizer, and possibly Sequella. Treatment with three new drugs, instead of just one, is expected to ensure both adequate treatment and prevention of resistance development. The goal is to provide real help to patients with treatment-resistant forms of TB as soon as possible, while simultaneously gathering intensive data on outcomes with long-term follow-up. This proposed global study of combinations of new chemical entities at select centers of care is expected to have only a marginal incremental cost compared with traditional, individual compassionate use and expanded access programs.[137]

With drugs in late-stage clinical development, sufficient efficacy, safety, and pharmacokinetic data exist or will soon exist to justify their compassionate use. However, there is unacceptable resistance within the TB establishment to allowing compassionate use. Regulators and controllers in many countries are reluctant to allow access to well-characterized compounds in development, opting instead to continue putting people on toxic fourth- and fifth-line drugs, which often have even less available evidence of safety and efficacy than do investigational drugs. Denying people with XDR-TB and pre-XDR-TB the chance to benefit from new drugs is, in many cases, a death sentence. Providing rational, expeditious preapproval access to new compounds—ideally in combination—is essential.

RECOMMENDATIONS

Pediatric and Maternal TB

Integrating TB screening and treatment for women and children into HIV and other health-service programs is a simple and efficient way to involve these often-neglected populations. In particular, IPT for children and pregnant women is often unavailable in many countries, and could be facilitated with a simple tool to improve IPT management in child contacts.[138,139] Research also needs to involve women, including pregnant and breastfeeding women, earlier and more often. Pediatric investigational plans for drug development need to involve children—including very young children—as early as safety permits. The timely development of pediatric-friendly formulations and FDCs will facilitate the earlier inclusion of children in research and the appropriate administration of treatment in programmatic settings.

Regulatory Requirements

Stringent regulatory authorities should consider logical and innovative clinical trial study designs such as symptomatic and microbiological endpoints to make drug development more efficient. Regulatory authorities in countries with high TB burdens need to streamline their clinical trial– and drug approval processes to allow their constituents to access the life-saving benefits of crucial research and new drugs, once developed.

TB Elimination

TB research and programmatic efforts have led to major advances in the fight against tuberculosis. Combination studies are revolutionizing the TB drug development paradigm, and two drug candidates from novel classes are poised for registration. Operational research has demonstrated the role of case finding, preventive therapy, and TB/HIV service integration in reducing TB. A recent study showed that there was an association between increasing investments in national treatment programs and improved performance in reducing the TB burden in the 22 high-burden countries.[140] However, a perilous funding climate threatens these advances. Sustained—and indeed increased—political will to fight TB is necessary. The TB community—including researchers, sponsors, donors, multilateral policy makers, regulators, implementers, TB-infected individuals, and TB-affected community advocates—needs to continue building momentum to not just control, but finally eliminate TB.

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THE TUBERCULOSIS VACCINE PIPELINE

By Richard Jefferys

The human immune system and *Mycobacterium tuberculosis (M. tb)*, the causative agent of tuberculosis (TB), are ancient adversaries. *M. tb* DNA has been detected in skeletal and mummified samples dating back to thousands of years BCE.[1] As it stands today, the two sides have reached an imperfect, partial détente. The vast majority (~90%) of infected individuals resist disease through immunologic mechanisms that are only partly understood, but a significant proportion go on to develop active TB disease. The risk of active disease is greatly increased among those with immune deficiencies; while the lifetime risk is normally around 10%,[2,3] it can exceed 10% per year for HIV-positive people.[4]

The goal of vaccination is to improve the immune response to TB and reduce the incidence of active disease, either by enhancing control of the infection or preventing it entirely. Early last century, it was hoped that an attenuated version of a related organism, *Mycobacterium bovis bacille Calmette–Guérin* (BCG), would be effective. But while BCG remains the only licensed TB vaccine, it has turned out to offer highly variable and generally inadequate protection against the most common pulmonary form of the disease. BCG remains in use in many parts of the world due to its ability to protect against disseminated forms of TB during childhood, however it is no longer recommended for HIV-positive children due to the risk of disease from the vaccine itself.[5]

The partial efficacy of BCG is evidence that a TB vaccine is possible, but there is an urgent need to develop superior approaches. It has been estimated that even a 60% effective candidate could reduce TB incidence approximately 80% by 2050.[6] Yet society has been slow to recognize this urgency—as of the early 1990s, the pipeline of new TB vaccine candidates was completely empty. The situation has improved considerably over the past two decades, with much of the initial impetus coming from a workshop entitled "Blueprint for Tuberculosis Vaccine Development" chaired by scientist Barry Bloom in 1998.[7]

There are currently 12 new TB vaccine candidates in human trials, and the work begun at the 1998 workshop has been updated with the release earlier this year of "Tuberculosis Vaccines: A Strategic Blueprint for the Next Decade," a collection of papers that were initiated by discussions at the 2nd Global Forum on TB Vaccines in Tallinn, Estonia, in 2010 and published in the journal *Tuberculosis* in March 2012.[8] The process that led to the updated blueprint was coordinated by the World Health Organization's (WHO) Stop TB

Partnership's Working Group on New Vaccines, and supported by the WHO, the Bill & Melinda Gates Foundation, Aeras, the TuBerculosis Vaccine Initiative (TBVI), and the U.S. National Institutes of Health (NIH). The stakeholders involved are now meeting on a more regular basis, with the 3rd Global Forum on TB Vaccines scheduled to take place March 24–27, 2013, in Cape Town, South Africa. Although still under-resourced, the field has benefitted from an influx of over US$600 million in funding in the period 2005–2010.[9]

Over the past year, two new TB vaccine candidates have entered clinical trials, and there have been other signs of progress. Most notably, there are an expanding number of collaborations among stakeholders that will facilitate future research. These include:

- Discussions between Aeras and the mining conglomerate Anglo American to explore the possibility of TB vaccine trials in the latter company's South African mines, where workers face the world's highest risk of the disease;[10]
- A collaboration between the National Institute of Allergy and Infectious Diseases (NIAID), Aeras, and the company Crucell N.V. that will leverage NIAID's clinical trial infrastructure to provide additional sites for a pediatric study of the AERAS-402/Crucell Ad35 candidate TB vaccine as a booster immunization to BCG;[11] and
- A strengthened collaboration between Aeras and the European-based Tuberculosis Vaccine Initiative (TBVI) that will work to implement the recommendations of the new strategic blueprint for TB vaccines.[12]

The Vaccine Clinical Pipeline

There are two broad categories of vaccines under study: replacements for BCG that aim to be safer and more effective, and several approaches to boost immune responses to selected TB antigens. As yet there are no clear correlates of immunity to TB—a problem similar to that faced by HIV vaccine developers—so candidates face a long and costly journey through the pipeline, culminating in large-scale trials to prove efficacy. It has been proposed that it may be possible to test the ability of vaccine-induced immune responses to control a BCG challenge in humans, which could potentially help identify correlates of protection, but this model is still in the early stages of development.[13] Current knowledge regarding protective immune responses to TB, and their application to vaccine development, are the subject of an excellent and comprehensive recent review by Tom Ottenhoff and Stefan Kaufmann in the open access journal PLoS Pathogens.[14]

TABLE 1. TB Vaccine Candidates in Clinical Trials (as of July 2012)

Agent	Strategy	Type	Sponsors	Status
MVA85A/ AERAS-485	Prime-boost	Viral vector	Oxford-Emergent Tuberculosis Consortium/Aeras	Phase IIb
AERAS-402/ Crucell Ad35	Prime-boost	Viral vector	Crucell N.V./Aeras	Phase IIb
GSK M72	Prime-boost	Recombinant protein	GlaxoSmithKline Biologicals/Aeras	Phase II
RUTI	Immunotherapeutic	Fragmented MTB	Archivel Farma	Phase II
VPM1002	Prime	Recombinant live	Vakzine Projekt Management GmbH/ Max Planck/TBVI	Phase Ib
HyVac4/ AERAS-404 (SSI/ SP H4-IC31)	Prime-boost	Recombinant protein	Statens Serum Institute/Aeras/Sanofi Pasteur/Intercell	Phase I
Hybrid-1 + IC31	Prime-boost	Recombinant protein	SSI/TBVI/Intercell	Phase I
Hybrid-1 + CAF01	Prime-boost	Recombinant protein	SSI	Phase I
Ad5Ag85A	Prime-boost	Viral vector	CanSino Biotechnology Inc./ Aeras	Phase I
SSI H56-IC31	Prime-boost	Recombinant protein	SSI/Aeras/Bill & Melinda Gates Foundation	Phase I
ID93 + GLA-SE	Prime-boost	Recombinant fusion polyprotein	Infectious Disease Research Institute	Phase I

MVA85a/AERAS-485

MVA85A/AERAS-485—a recombinant attenuated version of the vaccinia virus (cowpox) combined with TB antigen 85A—is among the most clinically advanced TB vaccines. It was developed at Oxford University and is being evaluated as a booster of preexisting immune responses to antigen 85A, which are present in most people either as a result of BCG vaccination or natural exposure to TB. Phase I and II safety studies indicate that the vaccine has an acceptable safety profile; the most common side effects include local site of injection reactions and flu-like symptoms. Published immunogenicity results show induction of CD4 T-cell responses, which have generally been long-

lasting and show a polyfunctional profile (meaning an ability to secrete multiple cytokines).[15] Findings from studies in HIV-positive individuals are similar, but the CD4 T-cell responses have tended to be of lower magnitude and less durable. HIV status does not affect the safety of the vaccine, and—in collaboration with the Vaccine Research Center at NIH—the researchers have demonstrated that antigen 85A-specific CD4 T cells induced by the vaccine do not become preferentially infected by HIV.[16]

Aeras has partnered with the Oxford-Emergent Tuberculosis Consortium Ltd. (OETC) on a phase IIb efficacy trial of this candidate in infants that completed enrollment in April 2011. A second phase IIb efficacy trial in HIV-positive adults, funded by the European and Developing Countries Clinical Trials Partnership (EDCTP), is now under way. The OETC, a joint venture between the University of Oxford and Emergent BioSolutions Inc., has the rights to fully commercialize the vaccine, and Aeras will have the rights to distribute the vaccine to resource-limited populations for humanitarian purposes.

AERAS-402/Crucell Ad35

AERAS-402/Crucell Ad35 comprises a replication-deficient adenovirus serotype 35 (Ad35) that serves as a viral vector—a virus modified to deliver TB genetic material—for DNA-expressing TB antigens 85A, 85B, and 10.4. Aeras and Crucell N.V., a Dutch biopharmaceutical company that focuses on developing adenovirus-based vaccines for infectious diseases, are developing this vaccine candidate. Adenoviruses are unusually potent inducers of CD8 T-cell responses, which are considered an important component of immunity to TB and many other infections.

When given in adults after priming with BCG, AERAS-402/Crucell Ad35 has been shown to induce polyfunctional CD4 T cells and strong CD8 T-cell responses that were fifty fold higher than those detectable pre-boost (the highest magnitude CD8 T-cell responses seen with any candidate to date).[17] A phase IIb proof-of-concept clinical trial in HIV-negative infants ages 16–26 weeks is ongoing. The study includes an initial dose-finding period, followed by a safety and efficacy phase that will recruit over 4,000 infants (the recently announced collaboration with NIAID is providing additional sites for this trial). A phase II trial evaluating the safety and immunogenicity of AERAS-402/Crucell Ad35 in HIV-infected, BCG-vaccinated adults with greater than 350 CD4 T cells was initiated in 2009, but is currently on hold pending additional funding.

GSK M72

GlaxoSmithKline (GSK) is working with Aeras to conduct phase II studies of GSK M72, a recombinant protein vaccine combined with a proprietary adjuvant, AS01. Early results show that the vaccine is well tolerated and induces robust polyfunctional CD4 T-cell responses against the M72 antigen that have persisted for at least three years, but no CD8 T-cell responses. No serious adverse events have occurred; the main side effects are transient local injection-site reactions.[18] A phase II study assessing the safety and immunogenicity in HIV-positive adults with or without ART in TB endemic areas has closed to recruitment but continues to follow participants. Another ongoing phase II trial in Taiwan is assessing the impact of the vaccine in HIV-negative individuals who have received, or are currently receiving, treatment for active TB.

RUTI

RUTI is a killed TB vaccine originally discovered at Institut Germans Trias i Pujol and now being developed by the biotech company Archivel Farma. The vaccine is being evaluated for its potential to accelerate the treatment of latent TB infection in combination with isoniazid. A phase II study that compared three different doses of RUTI given after one month of isoniazid in HIV-positive and HIV-negative adults has been completed. The vaccine was well tolerated, with the most common adverse events being mild injection-site reactions. No effects on CD4 T cell counts or viral load were observed among HIV-positive participants. The vaccine induced long-term memory T-cell responses to multiple TB antigens.[19] Based on these results, a single injection of a 25 μg dose has been selected for evaluation in a proposed phase III efficacy trial to evaluate whether vaccination after six months of isoniazid can reduce the incidence of active TB among HIV-positive individuals with latent TB infection.

HyVac4/AERAS-404 (SSI/SP H4-IC31), Hybrid-1 + IC31, Hybrid-1 + CAF01, and SSI H56-IC31

The Statens Serum Institute (SSI) is a Danish research institution developing several TB vaccine candidates. The SSI strategy involves the use of protein subunits comprising different TB antigens combined into fusion molecules. These vaccines are currently being tested in combination with different adjuvants.

HyVac4/AERAS-404, also referred to as SSI/SP H4-IC31, uses SSI's H4 antigen (a fusion protein of 85B and 10.4) combined with Intercell's IC31 adjuvant. SSI is partnering with Aeras, TBVI, Intercell, and Sanofi Pasteur to develop this construct. Aeras is currently conducting a phase I trial in healthy adults.

Hybrid-1 contains the TB antigens 85B and ESAT6, and has been studied in combination with either IC31 or CAF01 adjuvants. With IC31, it has been shown to induce memory T-cell responses that were maintained over 2.5 years of follow-up in BCG naive volunteers,[20] and it also enhanced TB-specific immune responses in a study including individuals with prior BCG vaccination or TB infection.[21] A phase IIa trial of Hybrid-1 with IC31 is being planned.

SSI has published promising preclinical data on its newest candidate that includes a novel latency-associated TB antigen, Rv2660c, along with Ag85B, ESAT-6, and the IC31 adjuvant.[22] Dubbed SSI H56-IC31, this vaccine is now being tested in a phase I trial in humans. The trial is being conducted in collaboration with Aeras and is supported by the Bill & Melinda Gates Foundation Grand Challenge #12 consortium.

VPM1002

VPM1002 is a live vaccine made from a genetically modified BCG strain. The vaccine was originally created by the Max Planck Institute for Infection Biology and is now being developed by the company Vakzine Projekt Management. The vaccine has been shown to be safe and immunogenic in a phase Ia trial in Germany and a phase Ib trial in South Africa. The next step is a phase II evaluation of safety and tolerability of the vaccine among HIV-unexposed, BCG-naive newborns in South Africa.[23]

Ad5Ag85A

Ad5Ag85A is another adenovirus-based vaccine that employs serotype 5 (Ad5) as a vector to deliver the antigen 85A. Originally the brainchild of Zhou Xing from McMaster University in Hamilton, Ontario, the rights to further develop and commercialize this candidate were acquired by the Chinese company CanSino in August 2011. CanSino is now partnering with Aeras on this work.[24] A phase I safety and immunogenicity study in BCG-vaccinated and -nonvaccinated healthy adults is under way in Canada.

ID93 + GLA-SE

ID93 + GLA-SE is a new TB vaccine candidate developed by the Infectious Disease Research Institute (IDRI) in Seattle. The construct comprises a recombinant fusion polyprotein including four TB antigens (Rv2608, Rv3619, Rv3620, and Rv1813) delivered together with an adjuvant named GLA-SE. IDRI recently announced a new partnership with Aeras to develop this candidate,[25] and a phase I trial is scheduled to start in June 2012.

Conclusion

The TB vaccine pipeline in 2012 appears relatively healthy but, as in many other areas of research, the global economic downturn is casting a dark cloud of concern over the future. The Treatment Action Group and Stop TB Partnership's 2011 report on funding trends for TB research and development documented a dismaying 29% drop in vaccine research funding from US$110 million in 2009 to US$78.4 million in 2010. These levels fall woefully short of the estimates contained in *The Global Plan to Stop TB 2011–2015*, which suggest that US$1.9 billion will be required over this period.[26] Vigorous advocacy will be required in order to address this shortfall, and ensure that an efficacious TB vaccine is developed.

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