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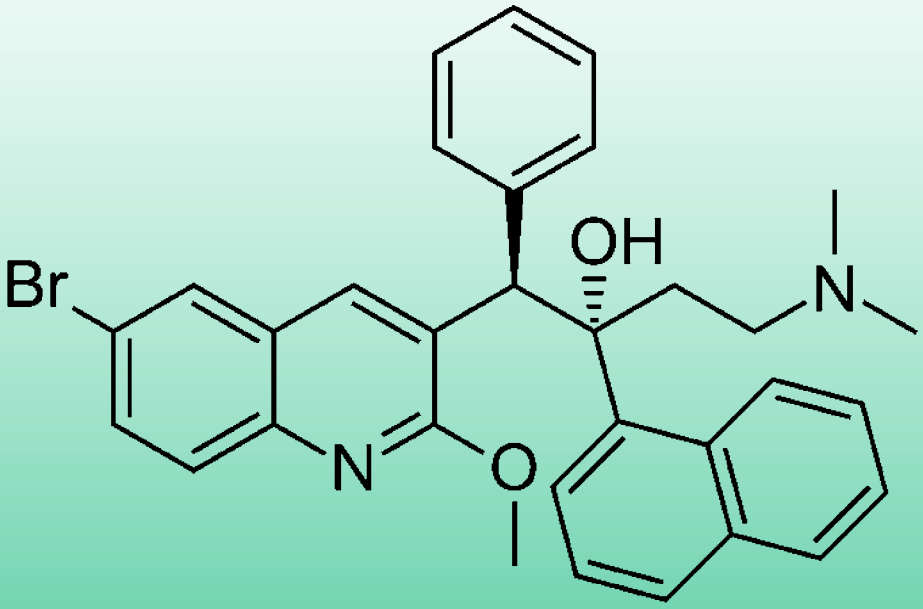
TAG
Treatment Action Group

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

2011 Pipeline Report

Second Edition



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WITH A CONTRIBUTION BY JONATHAN BERGER

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.

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THIS REPORT IS DEDICATED TO

HIV and Human Rights Activist

Dr. Robert Carr

(d. 2011)

and

Ugandan LGBT Activist

David Kato Kisule

(1964–2011)

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Introduction and Executive Summary

BY POLLY CLAYDEN AND MARK HARRINGTON

As this i-Base and TAG *2011 Pipeline Report, Second Edition,* makes clear, medically, the prospect for people with HIV, hepatitis C virus (HCV), and tuberculosis (TB) to live long and healthy lives—and in the cases of HCV and TB, to be cured rapidly with safe, effective, oral combination therapy—has never been better.

Politically and economically, the world's activists and political leaders face a crisis in which the former must persuade the latter to redirect billions of dollars from unproductive wars into life-saving health research and access programs, at home and internationally.

Here we will summarize the exciting progress that appears later in this report in great detail, and will look in greater depth at the last and the next decades of HIV treatment research.

Globally, 34 million people are living with HIV infection, an estimated 2 billion with latent *Mycobacterium tuberculosis* (TB) infection, and up to 130 million with chronic HCV infection.

At least 1.8 million people died from AIDS in 2009, one quarter of them from TB, which on its own killed 1.7 million people. There is neither global nor national surveillance for HCV-related illness and death, but more than 300,000 people die from HCV complications each year, and HCV mortality will continue to increase in the coming decade.

HIV infection can be controlled with lifelong triple-combination antiretroviral therapy (ART). Latent TB infection can be treated with six to nine months of isoniazid (INH) or 12 weeks of once-weekly rifapentine and INH. Active TB disease, if drug-susceptible, can be cured in 95% of cases with four drugs in six months, while drug-resistant forms of the disease can be cured up to 70% of the time if multidrug-resistant, or just 30% if extensively drug-resistant, with unpleasant combinations that can take up to two years to work, if they work at all. HCV is now curable in up to 75% of infected people with genotype 1 (predominant in major pharmaceutical markets) who have access to—and can tolerate—today's standard of care: triple therapy with pegylated interferon, ribavirin, and an HCV protease inhibitor.

As the writers of this report reveal, the prospects for dramatic—indeed in some cases revolutionary—changes in prevention and treatment for the three diseases in the next decade are amazingly good. Decades of high-quality research, increased investment, and growing and targeted community-based activism have set the scene for the possibility—for the first time since HIV/AIDS emerged in 1981—to make dramatic reductions in new HIV infections worldwide, while saving the lives of as many of the 34 million currently infected who can access therapy. Treatment is continually improving, with modern combinations dramatically less toxic, more tolerable, and easier to take than the first-generation ART combinations of the 1990s.

Simon Collins covers developments in the innovator antiretroviral (ARV) treatment pipeline, while Polly Clayden addresses the persistent, and as-yet-unfulfilled, needs of the substantial global population of infants, babies, children, and adolescents with HIV for appropriate and easy-to-use formulations of the best ARV drugs.

Contrary to the predictions of obstinate pessimists who constantly bemoan the imminent emptying of the ARV pipeline, Simon Collins demonstrates that the 2011 HIV treatment pipeline is robust indeed, with twelve agents and fixed-dose combinations (FDCs) in phases II or III, still more in phase I, and three new drugs or formulations already approved in the last year—the NNRTIs rilpivirine (Edurant) from Tibotec/J&J (although when this will be preferred in treatment-naive patients is unclear), Boehringer Ingelheim's extended-release formulation of nevirapine, Viramune XR (just in time for the patent expiry on the original), and the fixed-dose combination (FDC) of rilpivirine/tenofovir/FTC (Complera), from Gilead and Tibotec. Two new integrase inhibitors—elvitegravir and dolutegravir—are in late stages of development, both formulated in novel FDCs. This year's pipeline is at least as full as that of any other year documented by TAG in our annual ARV pipelines since 2003.

Polly Clayden provides an intriguing and expanded summary of the emerging field of point-of-care diagnostics research to make HIV-RNA (viral load) and CD4 cell-count testing available in decentralized settings where most people will receive their HIV treatment and care over the coming decade.

Although, as Jonathan Berger explains, the empty pipeline pessimists may be right for the global majority of people with HIV. For most people in developing countries, access to new drugs is hostage to a number of non-medical factors, particularly those related to intellectual property. In his chapter, Berger examines the global context that affects domestic patent laws. He also provides valuable insight into the licensing policies of companies with ARVs in the pipeline.

Also for the first time, researchers and activists are seriously pooling forces to mount a campaign to accelerate research to actually cure HIV infection. Richard Jefferys provides

a clear summation of the state of the art of HIV cure-related research. Jefferys also describes an encouraging duo of promising results from ART-related prevention strategies: the tenofovir gel–containing HIV microbicide used in the CAPRISA 004 study and the oral Truvada (emtricitabine/tenofovir) preexposure prophylaxis (PrEP) pill used in the iPrEx study in gay and transgender people. These results, taken together with the stunning 96% reduction in HIV acquisition among seronegative partners whose HIV positive partner received immediate ART at CD4 counts between 350-550/mm^3 in HPTN 052, constitute a seismic shift in biomedical HIV-prevention.

We eagerly await the results of the ongoing Strategic Timing of Antiretroviral Therapy (START) trial to further document the size and quality of the benefits of earlier ART initiation among treatment-naive persons entering with at least 500 CD4 cells/mm^3, which will complement those of HPTN 052 and clarify whether ART should actually be indicated at the time of HIV diagnosis for most, if not all, infected persons.

Jefferys continues his long-standing and detailed assessment of the HIV preventive- and therapeutic vaccine pipelines along with those for immune-based, cell-based, and gene therapy approaches to HIV treatment and functional cure.

In the case of HCV—as Tracy Swan's overview demonstrates—several generations of new direct-acting antivirals (DAAs) are in the pipeline, holding out the promise that it may be possible to cure people with oral drugs in the future. The HCV pipeline is robust. Currently, 14 HCV protease inhibitors (not including the just-approved boceprevir and telaprevir), 6 NS5a inhibitors, 10 non-nucleoside polymerase inhibitors, 8 nucleoside or nucleotide polymerase inhibitors, 3 host-targeting agents, 4 novel interferons, 3 immuno-modulators, a microRNA inhibitor, and an extract of milk thistle are in development.

If the promise of all-oral DAA cures is realized, the potential to roll out HCV treatment globally would then become dramatically easier, and hundreds of millions of lives could be saved. But most people with hepatitis C will not be cured—or even treated. The drugs are simply too expensive. New HCV treatments must be accessible to those who need them.

Swan warns that neither the health care system nor the provider community is ready to administer new and complex HCV regimens to an onslaught of newly diagnosed patients. Major adjustments will be needed to ensure that people with HCV—who often may need mental health care, addiction treatment, and HIV care and treatment—can be treated with dignity. Swan recommends the immediate establishment of a standing, multidisciplinary federal HCV treatment-guidelines panel—modeled in part after the very successful DHHS Antiretroviral Therapy Guidelines panels for adults, adolescents, and children—to review new data as they emerge, and to promulgate a coherent and up-to-date standard of care for all individuals with HCV.

Swan is critical of the pharmaceutical industry's failure to provide early-access trials and programs for people at risk for progression to end-stage liver disease. Preapproval access to new HCV drugs will save lives, and inform clinical practice in patients with urgent need. Swan is also dismayed that HCV drugs can come to market without information on how to safely and effectively use them during HIV treatment, with methadone, or in combination with other commonly used medications—or that coadministration may not be possible.

With TB, one of humanity's oldest and most stubborn pathogens, recent developments are encouraging but not yet revolutionary. A new, rapid, accurate, and sensitive TB test is now being rolled out worldwide which can diagnose the disease in two hours rather than two months. It works especially well in the forms of TB common among people with HIV infection, and it also detects drug-resistant TB. Proper deployment of this test could accelerate the identification and proper treatment of millions of people with TB disease. Its drawbacks include its price and requirement for electricity, and the lack (to date) of data to guide its use in children.

No new treatment has been approved to treat TB since the 1960s. For the first time in four decades, two new drugs from two new classes (TMC207 and OPC-67683) are likely to be submitted to regulatory authorities for approval in the coming year to treat multidrug-resistant forms of TB. Again, the potential gains in lives saved amount to millions.

Claire Wingfield and Richard Jefferys provide an encouraging assessment of recent developments in the slowly reviving TB vaccine research field, while Wingfield herself documents the results of the past decade of increasing investment in TB treatment, which is finally beginning to yield promising candidates. Javid Syed notes with dismay the sudden lull in development of new TB diagnostic tests after a brief spurt in the past four years—with the elusive TB point-of-care (POC) test still a distant aspiration—while the rollout of Cepheid's Xpert MTB/RIF TB and drug-resistance rapid molecular test has the promise of radically accelerating TB diagnosis and proper treatment initiation among persons with HIV-associated or drug-resistant TB. The next year will see extensive implementation science related to the rollout of Xpert MTB/RIF, while basic scientists and industry technicians continue their arduous, grossly underfunded search for a potential biomarker that could be used in a TB POC test.

Over the past decade, the public, private, and philanthropic sectors have invested tens of billions of dollars in HIV prevention and treatment research, hundreds of millions in HCV, and far less in TB, despite its prevalence, persistence, and toll on human lives. Clearly diseases that affect both rich and developing countries attract far more research investment than those predominantly confined to the latter. Political leaders and treatment activists alike have the obligation to redouble their efforts in the coming decade to

accelerate research that could end the pandemics of HIV, HCV, and TB. In the meantime, political leaders must redirect resources from wars and serial bank bailouts toward meeting the health needs of their own people and everyone else around the world.

A Golden Decade of Antiretroviral Drug Development

We believe it is worth exploring the past decade of ARV drug development for several reasons, including (1) to evaluate claims that the HIV drug pipeline is drying up; (2) to determine the success rate for ARV drug candidates entering phases II–III in order to assess the likelihood that current candidates will progress toward approval; (3) to examine the rapidity with which new drugs and combinations enter practice in one industrialized country, the United States; and (4) to discuss the relative potential of investments in studying lower doses of existing drugs versus expanding investment in new drugs and combinations.

The global ARV treatment market is estimated at $13 billion in market volume this year (Market Research News 2011), with most of the profits made in industrialized countries, while most of the people in need of treatment live in developing ones.

The past decade has indeed been a golden age of ARV drug development. Of the 30 new chemical entities approved by the U.S. Food and Drug Administration (FDA) to treat HIV infection since 1986, half (15/30) were approved in the years since 2003 (FDA 2011a). Thirty-five drugs and FDCs are FDA-approved for sale in the United States; a further 132 drugs and FDCs (including adult and pediatric formulations) are tentatively approved under the FDA's generic registration program to facilitate global access through programs such as the President's Emergency Program for AIDS Relief (PEPFAR) (FDA 2011b). Please see the data series from the TAG ARV pipelines dating from 2003 to the present (Table 1, pp. 6-7).

The success rate for new ARV drugs and FDCs that have entered phase II or further studies since 2003 is an astonishing 32.6% (15/46). Most recently in 2011 the FDA approved rilpivirine (Edurant), extended-release nevirapine (Viramune XR), and the FDC rilpivirine/TDF/FTC (Complera). Gilead is expected to file with regulatory authorities for approval of the integrase inhibitor elvitegravir, the pharmacokinetic booster cobicistat, and the FDC elvitegravir/cobicistat/TDF/FTC ("Quad") in the first quarter of 2012, with regulatory action likely later in 2012, which, if it leads to approval, would bring the success rate to 39.1% (18/46).

So much for those who say investing in HIV treatment is a bad bet.

TABLE 1. HIV Treatment Pipeline 2003–2011

Class	Drug name	Generic name	Brand name	Sponsor	2003
NRTI	SPD 754, AVX754, DOT	Apricatibine		Shire Biochem, Avexa	
NRTI	D-D4FC, DPC-817	Reverset		Pharmasset/Incyte	I
NRTI		Racivir		Pharmasset	
NRTI	ACH-126,443	Elvucitabine		Achillion	II
NRTI	DAPD	Amdoxivir		Gilead, Emory, RFS Pharm	IIb
NRTI	MIV-310, FLT	Alovudine		BI, Medivir, Beijing Mefuvir	II
NRTI	AG1549	Capravirine		Agouron/Pfizer	III
NRTI	FTC	Emtricitabine	Emtriva (2003)	Triangle/Gilead	approved
NRTI	PMPA, GS-7340 (TDF prodrug)			Gilead	
NRTI	OBP-601	Festinavir		BMS	
NNRTI	DPC-083, AI-183			BMS	II
NNRTI		Calanolide A		Advanced Life Sciences/Sarawak MediChem	II
NNRTI	TMC-125	Etravirine	Intelence (2008)	Tibotec	II
NNRTI	GSK-2248761/IDX889			GSK/Idenix	
NNRTI	TMC-278	Rilpivirine	Edurant (2011)	Tibotec	
NNRTI	BILR 355/r BS			Boehringer Ingelheim	
NNRTI			Viramune XR (2011)	Boehringer Ingelheim	
NNRTI	UK-453,061	Lersivirine		Pfizer	
PI	TMC-114	Darunavir	Prezista (2006)	Tibotec	I/II
PI	VX-175/GW-433908	Fosamprenavir	Lexiva (2003)	Vertex/GSK	approved
PI		Tipranavir	Aptivus (2005)	Boehringer Ingelheim	III
PI		Atazanavir	Reyataz (2003)	BMS	approved
PI	GSK-640385	Brecanavir		GSK	
FI	T-20	Enfuvirtide	Fuzeon (2003)	Trimeris/Roche	approved
CCR5RI	SCH-C, SCH 351125			Schering-Plough	I/II
CCR5RI	SCH D, SCH 417	Vicroviroc		Schering-Plough	
CCR5RI	UK-427,857	Maraviroc	Selzentry (2007)	Pfizer	I
CCR5RI/CCR2RI	TAK-652, TBR-652	Cenicriviroc		Takeda/Tobira	
II	MK-0518	Raltegravir	Isentress (2007)	Merck	
II	GSK-1349572	Dolutegravir		GSK/Shionogi/ViiV	
II	GSK-1265744			GSK/Shionogi	
II	GS-9137/JTK-303	Elvitegravir		Gilead	
Anti-CD4 Mab	TNX 355, Hu5A8	Ibalizumab		Tanox, Biogen, Taimed	I
AI	PRO 542			Progenics	II
AI	PRO 140			Progenics	
AI	BMS663068			BMS	
MI	PA-457, MPC-4326	Bevirimat		Panacos, Vitex, Myriad	
PK booster	GS 9350	Cobicistat		Gilead	
PK booster	SPI-251			Sequoia	
FDC	ABC/3TC		Epzicom (2003)	GSK	approved
FDC	FTC/TDF		Truvada (2004)	Gilead	
FDC	EFV/FTC/TDF		Atripla (2006)	BMS/Gilead	
FDC	RLV/FTC/TDF		Complera (2011)	Gilead/Tibotec	
FDC	ELV/CBS/FTC/TDF	Quad		Gilead	

Sources: Camp 2003–2006; Huff 2007; TAG 2008; Huff 2009; Collins 2010–2011.

2004	2005	2006	2007	2008	2009	2010	2011
I	Ib	Ib	II	II	II	discontinued	
I	II	discontinued					
	Ib	Ib	II				
II	II	Ib	II				
to Emory	to RFS II		II	II	II	discontinued	
				to Mefuvir			
III	discontinued						
							II
							II
discontinued							
	II						
II	II	III	III	approved			
					II	II	II
	I	II	III	III	III	III	approved
		Ib	II				
							approved
					II	II	II
II	III	approved					
III	approved						
	Ib	II	discontinued				
stopped							
I	II	II	II	III	III	stopped	
I	II	III	approved				
		I				I	II
		III	approved				
					II	II	III
					II		
	I	II	II	III	III	III	III
Ib	II	II	II	II	II	II	II
	Ib	Ib			II		
						II	II
I	Ib	II	II	II	II	discontinued	
					II	III	III
						III	
approved							
		approved					
						III	approved
						III	III

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

TABLE 2. U.S. ADAP Antiretroviral Market Share by Drug in 2009

Sponsor	Brand name	Generic name	Abbreviation	Class
Gilead	Atripla	efavirenz/emtricitabine/tenofovir	EFV/FTC/TDF	NNRTI+2NRTIs
Gilead	Truvada	emtricitabine/tenofovir	FTC/TDF	2NRTIs
BMS	Reyataz	atazanavir	ATV	PI
Abbott	Kaletra	lopinavir/ritonavir	LPV/r	PI
Merck	Isentress	raltegravir	RAL	II
Tibotec	Prezista	darunavir	DRV	PI
Gilead	Viread	tenofovir DF	TDF	NRTI
BMS	Sustiva	efavirenz	EFV	NNRTI
Gilead	Emtriva	emtricitabine	FTC	NRTI
All recommended first-line ARV drugs subtotal				
GSK	Epzicom	abacavir/lamivudine	ABC/3TC	2NRTIs
Abbott	Norvir	ritonavir	RTV	PI
GSK	Combivir	lamivudine/zidovudine	3TC/AZT	2NRTIs
GSK	Trizivir	abacavir/lamivudine/zidovudine	ABC/3TC/AZT	3NRTIs
GSK	Lexiva	fosamprenavir	APV	PI
BI	Viramune	nevirapine	NVP	NNRTI
Tibotec	Intelence	etravirine	ETV	NNRTI
Pfizer	Viracept	nelfinavir	NFV	PI
GSK	Ziagen	abacavir	ABC	NRTI
GSK	Epivir	lamivudine	3TC	NRTI
Roche	Invirase	saquinavir	SQV	PI
Roche	Fuzeon	enfuvirtide	T-20	FI
Pfizer	Selzentry	maraviroc	MVC	CCR5RI
BMS	Zerit	stavudine	d4T	NRTI
BI	Aptivus	tipranavir	TPV	PI
Merck	Crixivan	indinavir	IDV	PI
BMS	Videx/Videx EC	didanosine	ddI	NRTI
GSK	Retrovir	zidovudine	AZT	NRTI
Pfizer	Rescriptor	delavirdine	DLV	NNRTI
All other ARV drugs subtotal				
All ADAP drugs 2009 total				

Source: NASTAD 2011a

	2009 ADAP reported expenditures	2009 expenditures adjusted for missing	% of total	Year FDA approved
	$348,729,057	$376,753,577	26.96%	2005
	$236,929,054	$255,969,116	18.31%	2004
	$147,703,662	$159,573,405	11.42%	2003
	$72,149,642	$77,947,727	5.58%	2000
	$51,950,133	$56,124,943	4.02%	2007
	$44,983,885	$48,598,874	3.48%	2006
	$35,870,178	$38,752,794	2.77%	2001
	$28,472,290	$30,868,413	2.21%	1998
	$1,563,801	$1,689,471	0.12%	2003
	$968,351,702	**$1,046,278,320**	**74.86%**	
	$69,922,861	$75,541,993	5.41%	2004
	$53,948,036	$58,283,402	4.17%	1996
	$49,600,002	$53,585,951	3.83%	1997
	$31,622,256	$34,163,481	2.44%	2000
	$30,610,979	$33,070,934	2.37%	2003
	$20,823,184	$22,496,574	1.61%	1996
	$13,510,660	$14,597,402	1.04%	2008
	$13,024,714	$14,071,404	1.01%	1997
	$10,735,553	$11,598,282	0.83%	1998
	$8,218,373	$8,878,817	0.64%	1995
	$6,189,161	$6,686,533	0.48%	1995
	$5,323,713	$5,751,537	0.41%	2003
	$4,401,282	$4,754,977	0.34%	2007
	$1,983,721	$2,094,520	0.15%	1994
	$1,650,208	$1,782,822	0.13%	2005
	$1,526,234	$1,648,885	0.12%	1996
	$1,146,738	$1,238,892	0.09%	1991
	$831,340	$898,148	0.06%	1987
	$191,901	$207,323	0.01%	1997
	$325,260,916	**$351,351,877**	**25.14%**	
	$1,293,612,618	**$1,397,630,197**	**100.00%**	

Rapid Implementation and Uptake of New Therapies Provides Rapid Return on Investment

Another remarkable feature of the HIV treatment landscape is the rapidity with which new drugs and combinations are incorporated into the standards of HIV care in developed countries. In the United States, this process has been facilitated since the late 1990s by the establishment of the standing Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents and the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (http://aidsinfo.nih.gov/Guidelines/Default.aspx).

The Adult and Adolescent Guidelines panel meets monthly by teleconference, once yearly in person (usually at the annual retrovirus conference CROI), and issues updated online treatment recommendations at least annually, with changes highlighted in yellow to make navigating the ever-changing treatment landscape easier. A review of data generously provided by the U.S. National Association of State and Territorial AIDS Directors (NASTAD) demonstrates the astonishing fidelity of US AIDS Drug Assistance Program (ADAP) prescribing practices in 2009 to the most recent iteration of the US HIV treatment guidelines (Table 2, pp. 8-9).

Among the many striking features of the 2009 ADAP reported data on ARV usage are (1) 75% of sales were for drugs recommended as preferred first-line ART regimens in the federal guidelines (Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents 2009); (2) of the nine drugs and FDCs included among the US first-line recommendations, eight of nine were approved by the FDA in the past decade; just one (efavirenz) was approved in the 1990s; (3) two drugs approved in 2006 and 2007—darunavir and raltegravir, respectively—were approved by the FDA for a first-line indication less than two years after initial recommendation in salvage patients; (4) both of those drugs soon after were included by the US guidelines panel among the preferred recommended regimens for antiretroviral-naive patients; and (5) prescribing practice rapidly evolved to incorporate the newest data on the newest drugs.

These data demonstrate the effective interaction of research, regulation, normative guidelines, practice, and implementation in the United States, despite its highly fragmented health care system and the fact that those receiving treatment through ADAP are, by definition, not rich. However, the fact that over 8,000 people are currently on waiting lists to receive treatment through ADAP reveals that not all is rosy in the United States (NASTAD 2011b).

In any case, it is clear that HIV therapeutics has room for considerable improvement, and that improvements will be rapidly diffused and their investors will enjoy a substantial return on their investment.

We urge the World Health Organization (WHO) as well as national guidelines-defining groups in countries affected by HIV to urgently implement such forward-looking practices to ensure that people living with HIV everywhere have access to the best possible treatment options.

Less of the Old—or More of the New?

There is a fine balance between innovation and retrofitting. There is a lot of talk underway about "dose reduction" or "optimization" strategies to allow the cheaper and potentially less toxic use of certain existing and possible new drugs, as summarized in Table 3.

TABLE 3. Proposed Potential ARV Dose Reduction Studies and Savings

Drug	Drug Name	Dose Comparison	PPPY current	PPPY expected	3-year market impact ($MM)
AZT	zidovudine	600 mg vs 400 mg	$89	$60	$90-$289
d4T	stavudine	40 mg vs 20 mg	$25	$25	N/A*
TDF	tenofovir	300 mg vs 150 mg	$87	$63	$242
[GS 7340	TDF prodrug	150 mg vs 50 mg	$63	$22	$410]†
EFV	efavirenz	600 mg vs 400 mg	$63	$42	$117-$132
		600 mg vs 300 mg	$63	$31	$169-$208
RLV	rilpivirine	monthly depot injection @ <$15	?	$10	N/A¶
ATV/r	atazanavir/r	200 mg vs 100 mg	$355	$125	$392-$439
DRV/r	darunavir/r	600/100 mg vs 400/50 mg	$835	$335	N/A§
LPV/r	lopinavir/r	800 mg vs 665 mg	$440	$365	$203–$254‡
[rtv	ritonavir	100 mg vs 50 mg	$83	$42	N/A']
DOL	dolutegravir	50 mg vs monthly depot injection @ <$15	$15	?	N/A[2]

PPPY = per patient per year; $MM = millions of US dollars.

* shift from TDF ($65–$75 pppy) to d4T 20 mg ($25 pppy) resulting in considerable savings
[† TAG/i-Base estimate based on fixed cost of TDF API]
¶ replace EFV @ $30–$45 pppy
§ Shift from LPV/r to DRV/r in a cost-neutral manner
‡ Heat stable (Meltrex) formulation 120% more bioavailable than capsules
[' To be used with ATV or DRV]
[2] Could replace EFV or TDF @ $30-$75 pppy

Source: Adapted from Conference on ARV Dose Optimization, Clinton Health Access Initiative, John Hopkins University, School of Medicine. Meeting Summary; Prioritized Project Portfolio by ARV. Unpublished manuscript. Conference on Antiretroviral Dose Optimization, Alexandria, VA, 7-10 June 2011.

[i-Base/TAG interpolations enclosed within brackets]

A minimal requirement for a reduced-dose ARV drug to be considered for use in global guidelines directed particularly at resource-limited settings would include proof of efficacy and safety. ARV activity needs to be comparable to currently recommended drugs and combinations. The acceptable margins of reduced activity have yet to be defined. Safety for long-term use in places where laboratory capacity is nonexistent and clinical monitoring is minimal at best, will also have to be proven. Particularly where patients and their families/support groups will be required to provide pharmacovigilance.

Some dose-reduction strategies might well succeed and are justified by the potential to free up substantial sums to be spent on expanding the number of people able to receive treatment. However, we have serious concerns about the proposed dose-reduction study of stavudine (d4T), a drug that, though cheap to manufacture, is on its way out everywhere in the developed world and in many places in the developing one. While the proposed 20mg stavudine dose might be acceptable in a short-term 48- or even 96-week virologic endpoint study, many of its most serious side effects (such as peripheral neuropathy and lipoatrophy) would not necessarily emerge until after such a study was completed.

For these reasons, we do not believe the stavudine dose-reduction study should proceed. Activist pressure and research needs to focus on increasing access to safer cost-saving alternatives to stavudine.

Even greater savings could be achieved if the tenofovir prodrug GS 7340 could actually be given at 50 mg daily or less—studies are still underway to determine its dose moving forward. Since the current global best-price for TDF is about $87 (MSF 2011), bringing the volume of active pharmaceutical ingredient for tenofovir down by 5/6 might allow a lowest global price of $22 or less—lower than the putative 20 mg stavudine price of $25.

Other drugs in late-stage development such as the integrase inhibitor dolutegravir (50 mg once daily) also offer potential savings on manufacturing.

Developers are also considering novel manufacturing and delivery techniques such as nanoparticles—discussed further by Simon Collins below—and long-acting slow-release injectables, which could potentially be given monthly or even quarterly. These compounds will never develop without financial support that recognizes the potential impact they could have on global health.

Therefore, we believe a proper balance needs to be struck between repurposing old or existing drugs with a search for the lowest safe and effective dose, and investing in innovative discovery and delivery systems which could potentially lead to much better outcomes for all.

Conclusion and Recommendations

Just 40%, or 6 million, of the estimated 16 million HIV-positive people in need of immediate treatment are currently receiving it. Implementers of HIV treatment programs in developing countries are facing awkward decisions about the speed at which they will continue to enroll new patients into HIV treatment programs while maintaining recently enrolled ones. In addition to raising the enrollment bar to admit people with higher CD4 cell counts (up to 350 cells/mm^3 and in some cases higher), switching from stavudine-based to tenofovir-based first-line regimens, strengthening the quality of patient and laboratory monitoring, and expanding prevention and testing programs. All in the context of a gaping abyss of global leadership, flagging political commitment, and uncertain prospects for economic revival.

Activists, scientists, implementers, and political leaders are obliged to exert their utmost efforts to accelerate scientific progress and to save as many lives as possible in spite of the challenges we face. In this concluding section of the introduction to the *2011 Pipeline Report*, we highlight some of the most pressing priorities for research, access, and activism for HIV, HCV, and TB, emphasizing, when possible, opportunities for cross-cutting integration of efforts.

HIV

Despite the unprecedented progress in both research and access over the past decade, many unmet medical and public-health needs remain for future HIV treatments and programs.

Point-of-care diagnostics. The promise of universal access cannot be met without cheap, accurate, point-of-care diagnostic tests to diagnose HIV, stage patients for risk of opportunistic complications, and monitor response to therapy. Thus, intensified research efforts are required to accelerate the development, uptake, and rollout of point-of-care HIV diagnostics, and viral-load and CD4 tests.

Simple, safe, and durable daily FDCs. Unmet medical needs in the HIV therapy space are many. A cheap, daily (or less often) FDC that is super-potent, safe, tolerable, nontoxic, and with a high barrier to resistance—and that can be used in children, pregnant women, and those with TB—would make it possible to keep most people on first-line therapy for life (or until a cure is discovered and made readily available worldwide).

New anchor drugs. For adults globally, a new NNRTI (or a super-low molecular weight protease or integrase inhibitor) that spares the CNS, kidneys, lipids, and liver from currently common toxicities could be a great advance.

New backbone drugs. Something cheaper than tenofovir (TDF) would be good; a TDF prodrug such as GS 7340 could fit in nicely here. Novel nucleoside backbones which do not use tenofovir or AZT could be helpful, both for toxicity reduction and for greater strategic options in second-line therapy and beyond.

New pediatric drugs, formulations, and FDCs. Accelerated development of new drugs in appropriate pediatric formulations or FDCs for children of all age levels would help to close the gap between the quality and modernity of adult and pediatric HIV treatment.

Integration of ART-based prevention and treatment. With the recent breakthroughs on the microbicide, PrEP, and serodiscordant couples/early ART-initiation fronts, program implementers finally have a chance to end the sterile debates and bureaucratic fragmentation of HIV programs that fail to address testing, prevention, treatment, and care in an integrated and community-driven manner.

Complete the START trial. Given the results of HPTN 052, it is essential to complete the START trial to provide more quantitative and qualitative data on the risks and benefits of much earlier initiation of ART. And to answer, in sub-studies, questions on the impact of HIV on central nervous system (CNS) and bone health in early infection.

Invest in treatment for people currently resistant to existing drugs—for whom tolerability may be different from that of treatment-naive people—including the strategic development of new FDA-supported initiatives to study two or more compounds active against MDR-HIV together in joint fast-access protocols.

Invest in and accelerate research toward a functional and a sterilizing cure for HIV.

Continue to plug away at discovering and developing a truly effective preventive vaccine.

In the meantime, further validate ARV-based microbicides and PrEP, and figure out how to use them effectively in the real world.

The WHO should move much more rapidly to update its HIV treatment and prevention guidelines to respond to newly emerging data.

HCV

Establish national-level HCV treatment guidelines panels to regularly update the standard of care for HCV treatment based on the latest data. Prepare health systems, providers, and people with HCV for the rapidly coming day when HCV will be curable with all-oral DAAs.

Plan for global uptake and access to all-oral DAA cures once they are available.

TB

Substantially intensify investment in new TB diagnostics, drugs, vaccines, and operational research to support scale-up of new technologies. Accelerate discovery and development of a true TB POC test.

Encourage the entry of new sponsors in TB drug and vaccine development.

Prioritize development of pediatric formulations and FDCs for current and new TB regimens.

Study the safety of TB drugs in pregnant women.

Cross-link existing research infrastructure and develop new site and network capacity to more rapidly evaluate new TB treatment regimens and preventive vaccines.

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The Antiretroviral Pipeline

BY SIMON COLLINS

Introduction

This year the antiretroviral pipeline report is produced against the background of global economic problems that have steadily worsened, with few indications of imminent recovery, the impact of which threatens the goal of universal treatment in both rich and poor countries.

In the United States, the waiting list for State AIDS Drug Assistance Programs (ADAPs) has increased by 900% in a year to over 8,000 by June 2011. In addition, ADAPs have implemented cost-containment strategies, including reducing formularies, increasing the threshold for financial eligibility, instituting a CD4 threshold of <350 cells/mm^3, initiating waiting lists, and capping enrollment and access to the most expensive drugs. This bleak situation for uninsured or underinsured individuals who are otherwise ineligible for government assistance with antiretroviral therapy has so far been managed by patient assistance programs from drug manufacturers as a response to pressure from US activists in the Fair Pricing Coalition.[1,2]

In the UK, the public health care purchasers of HIV services in London (responsible for approximately 50% of HIV-positive people nationally) are seeking to contain national restrictions on National Health Service budgets by cost-saving from the drug budget. From April 2011, two-year contracts have been issued based on each manufacturer tendering bids for bulk volume purchasing. This aims to reduce use of antiretrovirals (ARVs) that have similar efficacy but are significantly more expensive, although treatment remains individualized and all licensed drugs can still be used based on clinical need. This policy was driven by the withdrawal of inflation linked funding and the need to find savings of £8–10 million.[3]

And last year a challenge to global access, in what was an otherwise hopeful and encouraging pipeline report, came with the first news that donors were restricting access to treatment for new patients in several countries.[4] Partly as a result of activist pressure enrollment caps were later removed from PEPFAR programs in Uganda.[5] Constricted health budgets in richer countries now politicize the choice between funding altruistic policies on global heath over those of providing health care for citizens at home.

Of course, in real terms, people in poorer countries are threatened most; they make up a broadly more marginalized demographic that is rarely prioritized for medical services. Despite this, right-wing health economists chose to propose that HIV funding has had a negative impact by dominating sponsor funding.[6, 7] In reality, the mobilization to focus on HIV, tuberculosis, and malaria has not only improved health investment in poor countries but has developed and strengthened the health infrastructure that was initially used as an excuse not to provide HIV treatment. Fortunately, each reactionary publication is vigorously rebutted with other articles and letters arguing the importance of the Global Fund to Fight AIDS, Tuberculosis and Malaria as a model for global health interventions.[8]

Consequently, new strategies are being formulated to try to prevent the potential health disaster that threatens to reverse the achievements of decades of prevention programs. In May 2011, the results from the HPTN 052 study added to accumulating data that quantify the significant impact of HIV treatment on reducing transmission—by 96% in people starting treatment with CD4 counts >250 cells/mm^3.[9,10] If the incentive of access to antiretroviral treatment is removed this will reduce the primary incentive for people to test and will drive HIV back underground.

Six million people now on treatment are returned to health, often starting from advanced HIV infection (CD4 counts <100 cells/mm^3).[11] However, less than 50% of people in need of treatment globally based on criteria of a CD4 count of <200 cells/mm^3 and 35% based on 350 cells/mm^3 currently access treatment. Additionally, at least half of the people on treatment are using drugs whose greater toxicity increases the risk of serious health complications. The World Health Organization no longer recommends stavudine (d4T) and the European Medicines Agency reassessed the use of stavudine in Europe to circumstances where its use was driven as a lifesaving emergency (specifically based on economic rather than health advantages),[12] yet d4T remains one of the most widely used nucleosides in antiretroviral combinations in poor countries. When data on side effects are collected, rates as high as 30–50% for irreversible peripheral neuropathy or lipoatrophy are commonly reported.

The demand for newer and more effective, efficient, safe, and affordable global treatment has never been greater. Western countries will remain a financially profitable market, but this is increasingly dependent on competitive rather than premium pricing.

This report summarizes results on pipeline compounds with promising future potential that have been presented in posters and presentations at key conferences. It is dependent on data that has passed some level of peer review, tempering the forward-looking statements of company press releases. It is limited to compounds that have cleared preclinical development and that have in vivo data in HIV-positive people.

Update from the 2010 Pipeline Report

Since last year's report, the only new chemical entity to be approved is the NNRTI rilpivirine (Edurant) in May 2011,[13] with a fixed-dose combination of rilpivine/tenofovir/FTC (Complera) from Gilead and Tibotec approved in August 2011,[14] for a U.S. Food and Drug Administration (FDA) indication for treatment-naive patients. An extended release formulation of nevirapine was also approved in March 2011.[15]

Gilead has completed and released 48-week data from ongoing phase III studies of a four-drug fixed dose combination (elvitegravir, cobicistat, tenofovir, and FTC), as it has with studies of the integrase inhibitor elvitegravir and the pharmacokinetic booster cobicistat. Additional pharmacokinetic and drug interaction studies have been reported for both compounds.[17,19]

Results from phase II studies of the integrase inhibitor dolutegravir (formerly S/GSK-572) in treatment-experienced patients were presented at the 18th Conference on Retroviruses and Opportunistic Infections (CROI) in February 2011, and planned phase III studies in treatment-experienced patients are now open.[20]

Phase II results for the NNRTI lersivirine in treatment-naive patients were presented at the International AIDS Society's (IAS) Conference in Rome, see below.

Phase II studies continue or are expected for an attachment inhibitor (BMS-663068), and a CCR5 inhibitor (cenicriviroc, formerly TBR-652).

Five compounds listed in last year's report as being in phase I studies have not visibly progressed, while three compounds had their development put on hold or discontinued: vicriviroc (a CCR5 inhibitor), GSK-761 (an NNRTI), and bevirimat (a maturation inhibitor).

Table 1 summarizes developments for the most important compounds highlighted in the 2010 pipeline report.

TABLE 1: Update on pipeline compounds in 2010 report

Compound	Company	Class	Stage	Update
rilpivirine	Tibotec	NNRTI	Approved	Filing submitted to FDA in July 2010 and approved for naïve patients in May 2011.[13]
rilpivirine/tenofovir/FTC (Complera)	Gilead/ Tibotec	Fixed-dose combination (NNRTI plus Truvada)	Approved	Filing submitted to FDA in November 2010 and approved for treatment-naïve patients in August 2011.[14]
elvitegravir	Gilead	Integrase inhibitor	Phase III	Ph3 48 week reached.[16]
cobicistat	Gilead	PK enhancer	Phase III	48-week Ph2 results comparing to ritonavir were presented at ICAAC 2010 and published in the 27 March 2011 edition of AIDS.[17, 19]
Quad	Gilead	Fixed dose combination (boosted integrase plus Truvada)	Phase III	48-week Ph2 results comparing to Atripla were presented at ICAAC 2010 and published in the 27 March 2011 edition of AIDS.[17, 18, 19]
dolutegravir (GSK1349572)	ViiV/ Shionogi	Integrase	Phase IIb	Ph2b data in 24 people with raltegravir-resistance reported at CROI 2011 using twice-daily dosing.[20]
GSK 2248761 (IDX-12899)	ViiV	NNRTI	Phase II	GSK announce that FDA put current development on hold due to toxicity concerns (four cases or seizure). No update since.[21]
UK-453061 (lersivirine)	ViiV	NNRTI	Phase II	No clinical update. Ongoing studies continue.[22, 23]
CTP-518	GSK	Protease inhibitor	Phase I	No update available.
BMS-663068	BMS	Attachment inhibitor (gp120)	Phase II	Two studies at CROI 2011.[24, 25]
Vicriviroc	MSD	CCR-5 inhibitor	Phase II/3	All development halted permanent in July 2010.[26]
Bevirimat (MPC-4326; was PA-457)	Myriad	Maturation inhibitor	Phase IIb	Development halted in June 2010.[27]
ibalizumab (TMB-355, was TNX-355)	TaiMed Biologics	CD4-specific humanised IgG4 monoclonal antibody.	Phase IIb	No updated information based on listed trials.[28]
cenicriviroc (TBR-652)	Tobira	CCR5	Phase II	Single one-dose PK study reported at CROI 2011. No new data. Ph2 study in naïve launched April 2011 (CVC +/- EFV vs efavirenz + Truvada).[29, 30]
CMX-157	Chimerix	NRTI similar to tenofovir.	Phase II	Minor update on Ph1 by press release.[31]
SPI-251	Sequoia	PK enhancer	Phase II	No further study results presented or trials listed.
PF-3716539	Pfizer/ViiV	PK enhancer	Phase I	No further data or new studies since acquired by ViiV but still listed in their pipeline.[32]
TMC558445	Tibotec	PK enhancer	Phase I	No further study results presented or trials listed.
TMC-310911	Tibotec	Protease	Phase I	No further reports. One 14-day Ph2 study listed as ongoing (from 2009).[33]

New Compounds First Reported in the Last Year

Several compounds first reported in vivo results this year and are summarized in Table 2.

GS-7340: A Prodrug of Tenofovir

GS-7340 is a formulation of tenofovir in development by Gilead that achieves higher levels of the active metabolite in lymph tissue and target cells including peripheral blood mononuclear cells (PBMCs) and has higher potency compared to equivalent tenofovir doses while maintaining reduced plasma concentrations (approximately 100-fold lower). The EC50 of GS 7340 against HIV-1 in MT-2 cells is 0.005 uM compared to 5 uM for tenofovir. This has the potential to require less active pharmaceutical ingredient (API), increase antiviral activity compared to tenofovir, and reduce systemic-related toxicity.

Results from the first dose-ranging study were presented at CROI 2011.[34] The double-blind study randomized 30 treatment-naive patients (CD4 >200; viral load >15,000) to either 50 mg or 150 mg of GS-7340 or to tenofovir 300mg (ratio 1:1:1). After 14 days these three groups produced time weighted viral load reductions of –0.95 (+0.32), –1.07 (+0.14) and –0.54 (+0.32) log10 copies/mL, respectively. Mean viral load levels dropped by –0.95, –1.57, and –1.74 log in the tenofovir, 50 mg, and 150 mg arms, respectively. Blood levels were lower (Cmax/AUC by 94%/88% with 50 mg and by 80%/58% with 150 mg) than the tenofovir group with PBMC levels approximately 30-fold higher.

There were no study discontinuations and no grade 3 or 4 events. Side effects reported were generally mild (nausea, headache).

The potential of this compound looks promising. It is unfortunate that it was not prioritized for faster development. In vivo data were presented on GS-7340 nine years ago at CROI 2002.[35]

Festinavir: An NRTI (previously OBP-601)

Festinavir is an NRTI with a chemical structure similar to stavudine (d4T), but which initial studies indicate should not have the same side effect concerns as it is a weak inhibitor of DNA synthesis in cell studies. BMS acquired development and marketing rights to Festinavir from Oncolys BioPharma in December 2010.[36]

Results from a phase Ib–IIa dose escalation study were presented as a poster at the 50th ICAAC in September 2010.[37]

Festinavir monotherapy was given for ten days to four groups of eight treatment-experienced patients currently not on treatment (each 6 active: 2 placebo) using once-daily doses of 100, 200, 300, and 600 mg.

Mean reductions in viral load at day 10 were 0.87, 0.98, 1.36 and 1.22 log10/copies/mL in the 100, 200, 300, and 400mg groups, respectively (vs -0.07 in the placebo group) from baseline levels that ranged from 4.2 – 4.6 log10 copies/mL.

No pattern of side effects appeared over 10 days with all grade 2–3 (n = 13) and grade 4 (n = 2) side effects judged unrelated to the study drug. No new reverse transcriptase mutations emerged at day 10 and 17.

In vitro data on the drug susceptibility of festinavir, including to the Q151M NRTI multidrug resistant mutation were presented in a poster at CROI in 2008.[38]

Although antiviral activity was reduced in presence of in 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 +/- M184V. Viruses carrying the Q151M mutation were hypersusceptible to OBP-601 (0.1- to 0.2-fold), even in the presence of K65R (0.3- to 1.3-fold).

TABLE 2: Compounds with first data presented during the previous year

Compound	Company	Class	Status	Comment	Reference
GS-7340	Gilead	NtRTI	Phase II	New formulation of tenofovir suggesting improved PK.	Abstract at CROI 2011.[33]
festinavir (OBP-601)	BMS	RTI	Phase II	Structurally close to d4T but hopefully without associated toxicity.	Abstract at ICAAC 2010.[36]

Update on Recent Approvals and Other Compounds in Development

This section includes a review of other compounds in further development.

Rilpivirine

Rilpivirine was approved in the United States in May 2011 for treatment-naive patients, based on 48-week results from the ECHO and THRIVE phase III studies and safety results from a phase II study out to 192 weeks.[39]

These studies, while reporting rilpivirine to be statistically non-inferior when compared to efavirenz, indicated less effective viral suppression when baseline viral load was >100,000 copies/mL with a higher risk of resistance in the context of treatment failure, and a greater loss of efficacy at lower than 95% adherence. These disadvantages were balanced by fewer side effects.[40, 41]

However, FDA approval is as a treatment for people who have not previously used treatment, when study results suggest use for an early switching of people with intolerance to efavirenz. The prescribing information highlights the poorer virological response at high viral load, and higher risk of resistance.

Rilpivirine is a 25mg tablet that needs to be taken once daily with food. Exposure is reduced by approximately 40% when taken fasted compared to with a normal meal or high-fat meal (defined as 533 kcal and 928 kcal, respectively). Exposures were reduced by 50% when taken with only a high-protein drink.

It was developed at a 25 mg dose due to phase II studies showing similar efficacy at 25, 50 and 75 mg and a caution over cardiovascular toxicity (QTc interval) at higher doses (75 and 150 mg). While the low dose offers exciting future potential for the development of coformulations, it results in a low pharmacokinetic threshold for people with poorer drug absorption.

The phase III studies had a similar design apart from use of background nucleosides. ECHO used tenofovir/FTC for all patients, and THRIVE allowed investigator choice. Each study randomized close to 700 treatment-naive patients without NNRTI or NRTI resistance. The primary endpoint was viral load suppression <50 copies/mL at week 48 (ITT-TLOVR analysis) with a lower margin of –12% difference for non-inferiority. Follow-up continues to week 96.

In the pooled analysis, baseline characteristics of the 1,368 patients included approximate median CD4 count 250 cells/mm^3 (range 1–1140), median viral load 5 log copies/mL (range 2–7), with just over 25% of patients having a previous AIDS diagnosis. Gender ratio was 75% male:25% female and mean age 36 years. Racial demographics were roughly 60% white, 24% black, and 12% Asian. Between 7% and 9% of patients were those coinfected with hepatitis B or C. Nucleoside choice in THRIVE was 60% tenofovir/FTC, 30% AZT/3TC, and 10% abacavir/3TC.

At week 48, suppression to <50 copies/mL was achieved in 84% versus 82% patients in the rilpivirine versus efavirenz groups (pooled results difference +1.6; 95%CI –1.7 to +8.8) with the lower bound for the confidence interval significantly above the pre-specified limit. CD4 increases were similar at +192 versus + 176 cells/mm^3, respectively.

Differences between the arms were more apparent when looking at reasons for treatment failure. In rilpivirine versus efavirenz, respectively, 9% versus 5% reported virological failure and approximately 2% versus 7% discontinued due to side effects. Around 5% patients discontinued from each arm for other reasons.

In the rilpivirine versus efavirenz groups, 5.5% versus 2.6% of people never suppressed to <50 copies/mL and 3.5% versus 2.2% patients who suppressed later rebounded.

No differences in virological response were reported by gender, race, geographical region, or nucleoside backbone. However, by baseline viral load the pooled response rates were 90% versus 84% (difference +6.6: 95%CI +1.6, +11.5) in favor of rilpivirine in the <100,000 group and 77% versus 81% (difference –3.6: 95%CI –9.8, +2.5) in favor of efavirenz in the >100,000 group. The vulnerability of the low dose was also reflected in the adherence analysis. Viral efficacy was similar between arms when adherence rates were reported as >95% and when viral load was low. However, when adherence dropped to less than 90% efficacy rates were lower with rilpivirine at both high and low viral loads.

People whose treatment failed on rilpivirine developed higher rates of both NNRTI-associated (63% vs 54%) and NRTI-associated (68% vs 32%) mutations. Rilpivirine was associated with the E138K mutation, with 90% of these patients showing phenotypic cross-resistance to etravirine, essentially losing the NNRTI class. People experiencing virological failure on efavirenz commonly developed K103N, which should retain sensitivity to etravirine.

Tolerability results favored rilpivirine with comparisons below for rilpivirine versus efavirenz. While >90% of patients in each arm reported at least one side effect, grade 2–4 events related to study drug occurred in 16% versus 31% ($p < 0.0001$) and discontinuations due to toxicity occurred in 3% versus 8% ($p = 0.0005$). Neurological side effects occurred in 17% versus 38% ($p < 0.0001$), psychiatric side effects in 15% versus 23% ($p = 0.0002$), abnormal dreams in 8% versus 13% ($p = 0.0061$) and rash in 3% versus 14% ($p < 0.0001$).

Grade 3-4 laboratory abnormalities occurred in 11% versus 18% patients ($p<0.001$), with higher rates of elevated ALT (1.5% vs 3.4%, $p < 0.05$) as well as increases in LDL cholesterol (0.7% vs 4.1%, $p < 0.0001$), triglycerides 0.3% vs 2.2%, $p < 0.001$), and total cholesterol (0.1 vs 2.5%, $p < 0.0001$), all favoring rilpivirine.

There was minimal change in mean serum creatinine in both groups, with no grade 3/4 creatinine increases and no discontinuations due to renal side effects or cases of acute renal failure. No difference was seen in changes in QTc interval between the TMC278 and efavirenz groups.

Several posters at CROI 2011 provided greater details on side effects and tolerability, again from pooled analysis of the same studies. While these generally show a broadly better profile compared to efavirenz, most side effects including central nervous system–related events are reduced rather than eliminated: rilpivirine has a similar profile to efavirenz, though just a little lighter. Some of the differences that are highly statistically significant may have limited clinical impact.

Lipid differences statistically favored rilpivirine over efavirenz, with greater increases in total cholesterol (TC), LDL cholesterol (LDLc), and triglycerides (TG) from baseline to week 48 reported with efavirenz compared to no significant changes in the rilpivirine group. No patients, however, discontinued treatment due to lipid changes. Grades 3/4 lipid-related abnormalities were lower with rilpivirine but also generally low in the study as a whole: TC (0.1% vs 3%, p ≤0.001), LDLc (1% vs 4%, p ≤0.001), and TG (0.3% vs 2%, p ≤0.001). These differences did not result in differences between the two groups in TC/HDL cholesterol ratio or cardiovascular risk as measured by the Framingham score.[42]

There were differences in the impact on vitamin D levels, measured as 25(OH)D (nmol/L). Mean (SD) baseline and week 48 reductions were statistically greater in patients using efavirenz: 61.8 (26.3) and 60.8 (22.8) [mean change -0.6 (17.9, p = 0.57] vs 64.1 (30.2) to 58.6 (26.9) [mean change -6.1 (18.0), p <0.0001]. The percentage of patients defined as severely deficient remained unchanged in the rilpivirine group at around 4.5% but increased from 5.2% to 9.0% (p = 0.03) in the efavirenz group.[43]

While neurological complications occurred significantly more frequently in the efavirenz arm, they still occurred in a significant proportion or patients using rilpivirine.[44]

Rilpivirine Fixed-dose Combination with Tenofovir/FTC

The new NNRTI-based fixed-dose combination of tenofovir/FTC/rilpivirine (Complera) from Gilead and Tibotec received FDA approval in August 2011,[14] with an indication for treatment-naive patients. Approval was based on bioequivilence to the individual drugs taken separately,[45] together with the phase III registrational studies for rilpivirine (ECHO and THRIVE) detailed above.

Alternative once-daily NNRTI-based single pill combinations clearly benefit patient choice but the efficacy results for this FDC suggest this would be most useful as a rapid switch option from Atripla for people with efavirenz-related side effects. Technically this might be considered to be off-label use unless the treatment-naive for the indication given for rilpivirine is interpreted as non-resistant.

Elvitegravir and Quad: Fixed-dose Integrase-based Combination

Clinical data on elvitegravir in treatment-naive patients includes 48-week results comparing two fixed-dose combinations—Quad (elvitegravir/cobicistat/tenofovir/FTC) versus Atripla (efavirenz/tenofovir/FTC)—were presented at ICAAC in September 2010.[16, 17, 18] This updated the 24-week (primary endpoint) results presented earlier at CROI 2010, which showed significantly faster viral responses in the integrase group.

Entry criteria included treatment-naïve patients with no documented resistance who were HBV/HCV negative. Baseline demographics included a mean age of 35, approximately 90% of participants were Caucasian, baseline CD4 was 389 versus 450 in the Quad versus Atripla groups and 4–6% had an AIDS diagnosis. However, mean baseline viral load was low at <40,000 copies/mL (4.6 log), and only 25% of people had levels >100,000 copies/mL.

Viral response rates at week 48 were the same as at week 24: 90% versus 83% (p = NS) of patients in the Quad versus Atripla groups respectively had an undetectable viral load (<50 copies/mL) at 48 weeks by intent-to-treat, missing = failure analysis. Mean CD4 increases were higher in the Quad arm at +240 versus +162 cells/mm^3.

Tolerability results also matched 24-week data: Quad was better tolerated in terms of lack of efavirenz-related side effects (35% vs 57% with any grade 1–4 drug-related adverse event). This was driven by reduced central nervous system toxicity.

A potentially new once-daily single pill integrase FDC will clearly improve patient options, but if approved, access and use in both first and second-line therapy, is likely to be widely dependent on its price being comparable to currently available options.

At the IAS in Rome, 48-week results were presented from Gilead's phase III non-inferiority study comparing elvitegravir favourably to raltegravir in treatment-experienced patients.[46]

Cobicistat

The pharmacokinetic booster cobicistat has so far reported similar boosting efficacy and side effects compared to ritonavir, without residual direct antiretroviral activity. Latest clinical data comes from elvitegravir studies (discussed above) and direct-booster comparison to ritonavir, both presented at the 50th ICAAC in September 2010. As with the studies on Quad in the same population, this showed that 24-week results were maintained out to 48 weeks.[16, 17, 18]

The comparator-booster study randomized treatment-naive patients to atazanavir boosted by either cobicistat (n = 50) or ritonavir (n = 29). At week 48, the percentage of patients with viral load suppressed to <50 copies/mL by intent-to-treat analysis (missing = failure) was similar with 82% in the cobicistat versus 86 % in the ritonavir groups (p = NS). Changes in mean estimated glomerular filtration rate (eGFR) at week 24 were similar and didn't develop with longer follow-up. Other grade 1–4 side effects were seen in 36% versus 48%, respectively. Changes in eGFR seen through 24 weeks were stable and similar to that seen in those receiving ritonavir. No additional discontinuations occurred between weeks 24 and 48: five versus three people in cobicistat versus ritonavir, respectively (relating to side effects in two people vs one).

The primary mechanism for boosting works through inhibition of the cytochrome P450 CYP 3A4. A study in HIV-negative volunteers using phenotype probes to investigate non–3A4-mediated interactions reported only weak inhibition of CYP2D6 and concluded that further interaction studies with metabolites of CYP2D6, CYP2B6, and the P-glyoprotein transporter (P-gp) would not be required.[47]

An agreement was also announced by Gilead on 28 June to collaborate on a co-formulation of cobicistat with Tibotec's darunavir. [48]

BMS-663068: An Oral Entry Inhibitor

BMS-663068 (BMS-068) is an entry inhibitor in development from Bristol-Myers Squibb active against the gp120 binding site on the CD4 cell. After oral administration this prodrug rapidly converts to BMS-626529, which reaches steady state after 2–3 days.

Richard Nettles from BMS reported results from a randomized open-label proof-of-concept study using BMS-068 in 50 people who were either antiretroviral treatment-naive (n = 34) or treatment-experienced but off treatment for the previous eight weeks (n = 16). Pharmacodynamic data were presented for 39 patients with an eligible IC50 <0.1 uM.[49]

The study included five dose combinations using BMS 068 1200mg once-daily and either 600 mg or 1200 mg twice-daily, with and without ritonavir boosting. Baseline demographics included median (range): CD4 432 cells/mm3 (206–921); viral load 4.4 log copies/mL (3.3–6.1); age 42 years (20–70).

After eight days most doses had reduced viral load by 1.6 logs (ranging from –1.22 to –1.78 in the intent-to-treat and –1.59 to –1.77 in the pharmacodynamic analysis). CD4 cell increases ranged from +28 to +106 after eight days. All patients with an eligible IC50 achieved viral load reductions of at least 1 log.

The pharmacokinetic data showed ritonavir to have a relatively modest impact on boosting BMS-068 and plasma levels of BMS-529 remaining 50-fold above median protein adjusted IC90 for twice-daily dosing and 9-fold above with the once-daily arm (with ritonavir).

All adverse events were grade 1 or 2 and were similar in each arm (though there was not a control arm). The most frequent side effects included headache (22/50, 44%) and rash (8/50, 16%), mostly mild. There were no drug discontinuations.

Detailed results were also available in a separate poster available online.[50]

A pharmacokinetic analysis of the dose response rate reported that the baseline EC90 as a marker for drug susceptibility has a stronger correlation to virological response that pharmacokinetic exposure and that EC90 values were wide in the monotherapy study (median 9.6 ng/mL, range 0.33 to >1860).[51]

Drug levels suggested that ritonavir boosting may not be needed, and phase IIb trials in treatment-experienced patients are planned to start later this year.

Dolutegravir: A New Integrase Inhibitor

Dolutegravir (previously GSK1349572) is in development by ViiV/Shionogi as a once-daily integrase inhibitor but overcomes resistance to raltegravir with twice-daily dosing. This makes this a key pipeline compound for use in multidrug-resistant patients.

Results from a second open-label phase IIb study of dolutegravir in people with raltegravir resistance were presented at CROI 2011.[52]

The dose-response rates from the initial use of a 50 mg once-daily dose of dolutegravir supported increasing the dose to 50 mg twice daily for this second cohort of treatment-experienced patients.

Baseline demographics included median (IQR): CD4 202 cells/mm3 (19–384); viral load 4.3 log copies/mL (3.9–4.8); age 47 (33–68); 75% male; duration on raltegravir 29 months (10–63). At baseline the median (range) fold change in susceptibility was >128 (0.8 to >128) to raltegravir and 2.7 (0.9 to 9.5) to dolutegravir. Baseline patterns of integrase-associated mutations were: N155H (n = 6); Y143H (n = 6); Q148+1 (n = 8); Q148+2 (n = 2); mixture (n = 1); other (n = 1).

The 50 mg twice-daily results included 24 people who added dolutegravir to a failing combination for 11 days (and who dropped raltegravir if they were still taking it). To be included in the study people needed to have at least one additional drug that would be

active, and this was added to dolutegravir on day 11 when the background combination was optimized, based on resistance test results.

Nearly all patients (23 out of 24) either reduced their viral load to less than 400 copies/mL or by at least 0.7 logs. The average (mean) drop in viral load at day 11 was –1.76 logs (SD 0.54) for the study as a whole and –1.57 for people with integrase mutations (Q148 + others). This compared to –1.45 logs seen in the initial 50 mg once-daily study.

Safety data were available for a median 96 days (range 30–172) mainly included common grade 1 or 2 gastrointestinal events not related to dolutegravir. Grade 3 laboratory abnormalities were reported in 4 people (17%) with no discontinuations. One participant had two serious events judged unrelated to the study drug (demyelinating polyneuropathy and diabetes mellitus). No grade 4 events were reported.

The 50mg twice-daily dose has now been selected for phase III studies in people who have integrase inhibitor resistance to raltegravir or elvitegravir. Phase III studies are also ongoing in integrase-naive patients.[53]

Forty-eight-week results from ViiV's phase II dose-ranging study of dolutegravir compared to efavirenz in treatment-naive patients were presented at the 2011 IAS in Rome.[54] These results were broadly similar to the 16-week virological and safety results presented at the IAS conference in Vienna in 2010. Dolutegravir and efavirenz achieved similar virological efficacy with differences between the two arms driven by slightly higher discontinuations related to efavirenz side effects.

Dolutegravir is also being coformulated in a fixed dose combination with GSK/ViiV nucleosides abacavir and 3TC. A phase III study in treatment-naive patients began recruitment in April 2011.[55]

Lersivirine: An NNRTI

Lersivirine (formally UK-453061) is an NNRTI previously in development at Pfizer and amalgamated into the ViiV antiretroviral portfolio, where development has not been prioritized over GSK's pipeline compounds.

A review of lersivirine was presented at the 10th International HIV Congress held in Glasgow in November 2010 focusing on the resistance profile.[56]

Viral load reductions of 1.6–1.8 logs were previously reported at the three higher doses of a 7 day monotherapy study in treatment-naive patients.

Lersivirine retained in vitro susceptibility (defined as <10-fold change in the IC50 of lersivirine) to 11 out of 19 viruses with multiple NNRTI resistance mutations that had significant loss of sensitivity to etravirine (>2.9-fold change; the lower clinical cutoff for etravirine) and to 5 out of 10 viruses (with >10-fold increase in IC50 for etravirine). Sensitivity to lersivirine was retained for many of the multiple mutations including Y181C. Additionally, the lack of correlation between resistance patterns for lersivirine and etravirine was reported to be consistent with their distinct mechanisms of action.

Forty-eight-week results were presented at the IAS for a dose-finding study comparing lersivirine to efavirenz in treatment-naive patients. The percentage of patients with viral load <50 copies/mL was 79%, 79% and 86% in the 500mg, 750mg and EFV groups respectively. Although the study was not powered to detect between arm efficacy 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). Overall, the combined safety analyisis reported a similar incidence of side effects in each group but fewer grade 3/4 events in the lersivirine groups (n= 2 and n=3) compared to efavirenz (n=8).[57]

Cenicriviroc: CCR5 and CCR2 Inhibitor (formerly TBR-652 and TAK-652)

Cenicriviroc is a CCR5 inhibitor with CCR2 activity in development with Tobira. CCR2 is associated with and studied in association with diseases related to immune activation.

Results from a 10 day dose-ranging monotherapy study in 54 treatment-experienced but CCR5-receptor blocker-naive patients were presented at the 18th International AIDS Society Conference in July 2010. Participants were randomized to 25, 50, 75, 100, or 150 mg cenicriviroc, all once daily, or to a placebo group. Inflammatory markers (MCP-1, hsCRP, and IL-6) were measured at days 1 and 10.[58]

Baseline median viral load was 4.5 log copies/mL (range 3.1–6.0), approximately 30,000 copies/mL, but this presumably limited the ability to detect maximum changes for patents starting with low viremia.

At day 10, viral load reductions of 1.4–1.8 log copies/mLwere seen in the 50–150 mg groups. Side effects were generally mild but were dose-related, and were higher in the 100 and 150 mg groups.

Although MCP-1 (a cytokine involved in immune inflammation) increased in all groups except placebo (significantly compared to placebo in the 50, 100, and 150 mg groups) this was only markedly higher for the 150 mg arm (by approximately 350 pg/mL).

Phase IIb studies of the compound are expected to start early in 2011.[20]

Other Research

Limited data available for other pipeline compounds are worth noting.

Apricitabine (ATC), an NRTI with a potential role in multiple drug resistance included in previous TAG reports was reinstated as a compound in development by Avexa, though no new data have been published.[59]

VIR-576 is a potential fusion inhibitor that targets gp41 that demonstrated mean antiviral activity of –1.3 log(10) copies/mL in treatment-naive individuals dosed at 5 grams/day (the highest of three dose studies) in a small phase I study. The current formulation, in development by Viro Pharmaceuticals, requires intravenous administration.[60]

Research continues into modification of antiviral human proteins including APOBEC that are active against HIV, but are neutralized by the accessory HIV viral protein Vif.[61, 62, 63] Preclinical studies reporting other potential new compounds that target HIV capsid, Tat inhibitors, RNase H inhibitors, gold-based compounds and numerous other targets are still in preclinical studies.[64, 65, 66. 67]

The development of new formulations of existing antiretrovirals is an exciting field.

Research-based companies have a long history of reformulating drugs and benefiting from extending patents. Generic formulations and fixed dose combinations have driven access to treatment globally through lower pricing for bulk purchasing and a wider choice of combinations.

For over a decade, generally small groups of scientists have developed numerous nanoformulations of current drugs.[68, 69]

This wide-ranging technology has the potential to improve on current formulation in many ways, including:

- Better bioavailability; as an example, this could be achieved by designing formulations that overcome hydrophobic or hydrophilic properties of individual molecules.

- Reducing drug wastage by overcoming protein binding during oral absorption, where >90% of the active compounds of antiretroviral drugs are cleared by blood filtration through the liver or kidneys before they are able to act on HIV.

- More targeted delivery should reduce the quantity of raw materials needed. This, in turn, has the potential to have the biggest impact on drugs used in resource-limited settings. Even though the drugs are much cheaper in poorer countries, a much higher percentage of the costs is related to APIs.

- Reducing toxicities related to the metabolism of current oral formulations. For example, if a nanoformulation is designed to increase active drug levels inside cells while keeping blood levels low this has the potential to reduce toxicities related to systemic drug levels.

- Sanctuary site penetration by developing formulations that target cells that cross the blood-brain barrier. In a similar way molecules may be designed to use cells to evade drug transporters such as P-gp that limit penetration of other sites.

Nanobased medicines are already used for other disease areas (including HIV-related complications), but despite the promising results in animal and cell line studies, this has not led to in vivo studies for antiretrovirals.

However, as we went to press, a pharmacokinetic safety study in HIV-negative adults of a pediatric nanosolution of efavirenz was due to start enrollment.[70] This encapsulation of efavirenz, otherwise poorly water soluble, into polymeric micelles of different poly(ethylene oxide)–poly(propylene oxide) block copolymers significantly improves oral bioavailability and reduces the interindividual variability. This solution has an improved taste, using only excipients approved by the FDA, and requiring less API has the potential to lower production costs.

Conclusion

Over the last two years a tangible policy shift towards finding a cure for HIV has reestablished the goals of a functional or therapeutic cure high on the research agenda. Like much else, this is driven by the sobering financial challenge of maintaining lifelong treatment for millions of people globally. However, despite the optimism for developing compounds that will target latently infected cells or selectively activate this resting pool, or for immune-based treatments that will maintain viral control without the need for antiretroviral drugs, an HIV cure seems unlikely to be fully realized within ten years.

New treatments will therefore remain in the management of HIV for the foreseeable future, and compounds highlighted in this review will hopefully progress to become licensed medicines. The HIV market in developed countries is continuing to increase annually and treatment in poor countries remains disturbingly less than universal. When approved, the cost of new drugs will drive most aspects of access in all countries.

New pathways still need to be constructed with regulatory support for developing drug options for people with multidrug resistance (MDR), including resistance to integrase inhibitors.

The potential to use an orphan drug designation is only one part of a solution. Rapid access to multiple investigational compounds, likely to be from different companies, is just as essential in order to protect against early failure in the population that is most vulnerable and most dependent on this research.

The requirements for a drug with MDR indication are different than one for use in treatment-naive patients or after early treatment failure because of the different risk-to-benefit ratio on viral efficacy compared to long-term tolerability.

Funding and resources need to be invested in technologies such as nanoformulations that have the potential to really treat HIV universally. This is especially important given the increasing data supporting medical benefits from starting treatment earlier in infection and the additional dramatic impact this has on onward transmission—and the wide gaps yet to be bridged to universal treatment.

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IAS: International AIDS Society
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The Pediatric Antiretroviral Pipeline

BY POLLY CLAYDEN

Fewer antiretroviral options exist for children than for adults. Last year's *Pipeline Report* introduced a new chapter looking at pediatric formulations of antiretrovirals.[1] The chapter detailed some of the hurdles to be overcome to ensure access to antiretrovirals in appropriate forms for children with HIV. It also showed some recent advances.

Since last year's report, new pediatric development has been scant. Despite incentives and penalties from regulatory authorities to innovator manufacturers designed to ensure that children benefit from these drugs, the disincentives to develop and produce them are considerable. Pediatric drug markets are generally smaller and less interesting to industry than those of adults. In rich countries pediatric HIV has been almost eliminated, meaning there is decreasing demand in these markets.

The best way to deal with pediatric HIV is to prevent it from happening in the first place. At present the elimination of mother-to-child transmission continues to elude most poor countries. Paradoxically, if maternal health and prevention of mother-to-child transmission (PMTCT) programs become more effective, the advantages in child health this brings will reduce demand further in the pediatric antiretroviral market.

Children are also unaffected by the growing case to provide treatment as prevention.

All this not withstanding, there has been significant progress in recent years in terms of both research and treatment scale-up. United Nations agencies, nongovernmental organizations (NGOs) such as Médecins Sans Frontières (MSF) and the Clinton Health Access Initiative (CHAI); and UNITAID and other major donors have made a concerted effort to highlight children with HIV and ensure that they have access to the medicines they need.

However, an analysis of the global pediatric antiretroviral market performed in 2010 revealed only a few generic fixed-dose combinations (FDCs) in solid and dispersible forms quality certified by the World Health Organization (WHO) Prequalification Programme or the US Food and Drug Administration (FDA) since 2005.[2] One quality-certified manufacturer produced most (67%) of these FDCs, and they combine only older antiretrovirals. UNITAID accounted for 97–100% of 2008–2009 FDC market volume.

Price reductions for pediatric FDCs do not have the same potential as those for adults due to small volume. The analysis reported low uptake of FDCs, but this is likely to be largely due to the time required to register products and phase out syrups rather than countries not wanting to use them.

Meanwhile, in 2009 an estimated 2.3 million children were living with HIV. Although an impressive 355,000 children started antiretrovirals that year, 370,000 were newly infected. HIV kills 700 children every day.[3]

Data produced by CHAI, as part of an internal review, illustrate the pediatric antiretroviral development inertia.[4] They show that pediatric determination (PD)—which occurs when manufacturers have completed all FDA requested studies and pediatric exclusivity is awarded—took an average of 6.5 years to achieve after approval for use in adults. This ranged from a laudable less than a year for abacavir to a spectacularly sluggish 14.9 years for saquinavir, which was never approved for children (see Table 1).

TABLE 1. Time frames between adult approval and PD for antiretrovirals with pediatric exclusivity

Drug	Calendar years	Time in years between adult approval and PD	Manufacturer
Didanosine	1991–2001	9.9	Bristol-Myers Squibb
Lamivudine	1995–2001	5.7	GlaxoSmithKline
Saquinavir*	1995–2010	14.9	Roche
Stavudine	1995–2001	5.7	Bristol-Myers Squibb
Ritonavir	1996–2005	9.3	Abbott
Nevirapine	1996–2001	5.5	Boehringer Ingelheim
Nelfinavir	1997–2003	6.5	Agouron
Abacavir	1998	<1	GlaxoSmithKline
Lopinavir/ritonavir	2000–2007	7.5	Abbott
Emtricitabine	2003–2005	2.9	Gilead
Tipranavir	2005–2007	2.7	Boehringer Ingelheim

Source: CHAI
*Still not approved

When drugs are approved for children, multiple label changes may take place because pediatric populations are studied in sequence. As pediatric investigation plans work in de-escalated age bands, the youngest age groups will have the most prolonged delay in labeling.

Sometimes there is no indication or appropriate formulation for the very youngest children, complicating the implementation of universal treatment as early as possible in infancy.[5]

Perhaps the most notable change since the *2010 Pipeline Report* is that Drugs for Neglected Diseases Initiative (DND*i*) has recently entered the field. That this organization considers pediatric HIV to be a neglected disease speaks volumes.[6]

This chapter gives an update on recent results from clinical trials that will help inform guidance, new approvals and contraindications, the generic and innovator pipelines, "ones to watch," and how the new drugs might be used.

What to Start With?

WHO guidelines recommend that young children less than two years who have been exposed to maternal or infant nevirapine or other non-nucleoside reverse transcriptase inhibitors (NNRTIs) for maternal treatment or PMTCT, start antiretroviral therapy with a lopinavir/ritonavir–based regimen. Nevirapine- or NNRTI -unexposed children, or children older than two years, should start with an NNRTI-based regimen of nevirapine, or efavirenz if the child is older than three years.

Nucleoside reverse transcriptase inhibitor (NRTI) backbones should be one of the following pairs: lamivudine plus zidovudine, lamivudine plus abacavir, or lamivudine plus stavudine. Stavudine is no longer preferred due to its toxicity.

Results from two recent studies may have an impact on future guidance with regard to the use of NNRTIs versus protease inhibitors (PIs) for younger children.

Findings from the IMPAACT P1060 study showed about 20% higher rates of failure at 24 weeks in children aged two months to three years receiving NNRTI-based regimens compared with those receiving PI-based regimens with or without NNRTI exposure.[7,8] These results are unsurprising for the NNRTI-exposed children. What is surprising and controversial is the superiority of the PI regimen for NNRTI-unexposed children in this trial—particularly for providers with experience in using NNRTIs in this population in resource-limited settings.

In reality, many caregivers in resource-limited settings prefer nevirapine first-line, even for children exposed to it in utero, due to cost constraints, ease of use, and to preserve lopinavir/ritonavir for second–line.

The NEVEREST trial, also recently presented, showed that children started on lopinavir/ritonavir–based regimens who remained on them had about 10% higher rates of virological failure than children switched to nevirapine.[9,10]

Currently, WHO guidelines remain unchanged from last year, and opinion differs as to whether it is better to start with a PI or an NNRTI for all young infants. It is argued that many children will still not have been NNRTI- exposed through PMTCT, but this is usually poorly documented. NNRTI-based regimens remain attractive because of cost constraints, formulation, and palatability. PI-based regimens are more potent and can be used in exposed or unexposed children. NEVEREST data suggest it may be possible to switch to an NNRTI after initial suppression with a PI, but this would depend on access to virological monitoring.

There is agreement, however, that current drugs are far from perfect and a suitable first-line agent, to fit with current guidance, could be a cheaper, more user-friendly PI or a more robust NNRTI suitable for exposed or unexposed children (see Table 2).

As far as older children are concerned, data from the PENPACT-1/PACTG 390 study showed no significant difference at four years with viral suppression with regimens containing either an NNRTI or a PI.[11] The PLATO II/Cohere study showed no difference in triple-class failure by initial regimen at four years of age in European children starting treatment with three or more antiretroviral drugs.[12]

TABLE 2. Use of NNRTIs compared to PIs in young children in resource limited settings

Variable	NNRTI	PI
Cost	Neviripine-based: US$55–209 per patient year	Lopinavir/ritonavir– based: $218–329 per patient year
Formulation	Several pediatric nevirapine-based FDCs	No three-in-one FDCs with lopinavir/ritonavir; heat-stable liquid must be used for very young children*; children over 10 kg may be able to use a 100/25mg heat-stable tablet (cannot be crushed)
Robust	Single-point mutation can confer resistance	Multiple mutations needed
Following NNRTI exposure for PMTCT	Not recommended	Recommended exposed or unexposed
Use with TB medicines	Efavirenz	Complicated: lopinavir requires extra ritonavir boosting or higher dose
Aligned with adults	Yes	Boosted PI is an adult second-line drug
All age groups	Yes, nevirapine. Efavirenz not recommended less than 3 years	Yes, lopinavir/ritonavir
Use second line	PIs	Second-generation PIs

Toxicity	Nevirapine: Rash Hepatoxicity Efavirenz: Increased lipids Central nervous system	Lopinavir/ritonavir: Increased lipids Gastrointestinal problems Premature infants at increased risk of toxicity associated with lopinavir/ritonavir oral solution†
Palatability	FDCs OK	Lopinavir/r liquid unpleasant bitter taste

*At temperatures higher than 25°C, the oral solution of lopinavir/ritonavir requires refrigeration. There are no stability data at temperatures higher than 25°C for lopinavir/ritonavir. Some providers cannot safely prescribe this to infants in households without a fridge.

† Sometimes called "baby grappa"! The lopinavir/ritonavir syrup contains 42% ethanol and 15% polyethylene glycol.

Induction/maintenance strategies (where people are started on very potent combinations of drugs which are then reduced in number once full viral suppression is achieved) are underexplored in children,—as are questions as to whether a child starting treatment in infancy can ever stop.

Data from several ongoing studies, which will give more information about these issues are still awaited:

- ARROW is investigating a strategy of induction/maintenance—starting with a potent combination of four drugs and maintaining treatment with three versus continual treatment with four drugs.[13]
- CHER, which demonstrated a big AIDS-free survival advantage from universally starting children on treatment at birth, will continue to follow these children's progress and look at whether after starting early they can stop treatment after one or two years.[14]
- BANA and PENTA 11 will determine whether taking CD4-guided planned interruptions disadvantages children on stable therapy.[15,16]

Recent Changes

New FDA Tentative Approvals and WHO Prequalifications

Since last year's *Pipeline Report* there have been a number of new tentative approvals and prequalifications (see Table 3).[17,18]

The good news is that there are several formulations that include abacavir, both stand-alone products and as part of FDCs. Not such good news is that the only PI included is nelfinavir powder, which is barely used in rich countries and is not recommended in guidelines.

TABLE 3. FDA tentative approvals (TA) and WHO prequalifications (PQ) of pediatric antiretrovirals, 2010–2011

Drug	Formulation and strength	Supplier/applicant	FDA TA	WHO PQ
Abacavir	Oral solution, 20mg/ml	Cipla	x	◦
Abacavir	Tablet, 60mg	Matrix	x	◦
Abacavir	Tablet for oral suspension, 60mg	Cipla	x	x
Abacavir/lamivudine	Tablet for oral suspension, 60/30mg	Cipla	x	
Lamivudine/stavudine	Tablet, 60/12mg	Cipla		x
Lamivudine/stavudine	Tablet, 30/6mg	Cipla		x
Lamivudine/zidovudine	Tablet, 30/60mg	Matrix	x	◦
Lamivudine/nevirapine/zidovudine	Tablet for oral suspension, 30/50/60mg	Matrix	x	◦
Nelfinavir	Oral powder, 50mg/1g	Cipla		x
Stavudine	Powder for oral solution, 1mg/mL	Cipla		x

• Formulations already prequalified by the WHO at the time of last year's review.

FDA Warning for Lopinavir/Ritonavir Oral Solution Use in Neonates

In February 2011, the FDA made changes to the Kaletra (lopinavir/ritonavir) oral solution product label to include a warning of potential toxicity in neonates. This was due to life-threatening side effects related to either lopinavir and/or the inactive ingredients propylene glycol and ethanol that had been seen in ten infants, eight of whom were preterm.[19,20]

This formulation should not be given to neonates before they are of a postmenstrual age (calculated from the first day of the mother's period until the baby's birth plus the time from the birth) of 42 weeks and a postnatal age of at least 14 days.

Reduced metabolism by the liver and reduced kidney function in newborns can lead to an accumulation of lopinavir as well as of alcohol and propylene glycol. Preterm babies may be at increased risk because they cannot metabolize propylene glycol.

This warning is important, as both maternal HIV and highly active antiretroviral therapy (HAART) are associated with preterm delivery (although infants exposed to maternal HAART are a small niche as very few infants will be infected if their mothers receive treatment).

Missing Drugs and Formulations

An important formulation in the generic pipeline at present is an alternative to the oral solution of lopinavir/ritonavir.

Cipla is developing a heat-stable sprinkle formulation of lopinavir/ritonavir that may fill this gap. This has been in development for a while now and has undergone a few changes. The sprinkles are tasteless and have a texture similar to granular sugar.

Bioequivalence studies are being undertaken in healthy adults. Pharmacokinetcs and tolerability studies comparing the sprinkles with liquid in 12-month- to three-year old children and with junior tablets in older children, up to four years old will be performed in CHAPAS 2.[21]

Acceptability of the formulation in young children is very important. The company is still deciding on how to package the 40/10mg dose. Cipla expects to apply for approval with the FDA at the end of 2011.

Darunavir is needed for third-line regimens or for second-line where lopinavir/ritonavir was used first-line. Preclinical studies—showing dangerously high darunavir exposure and in turn adverse events in juvenile rats—meant that pediatric studies were not conducted in children under three years old. Ritonavir boosting of darunavir does not lend itself to easily adjusted doses using WHO weight bands.

A 25mg tablet of ritonavir is included in WHO's Essential Medicines List but is not yet on the market.[22] A 25mg sprinkle formulation is needed for very young children. A 50mg tablet would be useful for super-boosting (giving extra booster to achieve sufficient drug concentration in circumstances where this is reduced by drug-drug interaction) PIs. Super-boosting PIs, when they are given with rifampicin, is not straightforward and urgently needs better guidance and better formulations.

Other generics in development for treating children or considered to be a high priority by the Pediatric Antiretroviral Group of the WHO are shown in Table 4. FDCs that are not stavudine based are also a priority.

TABLE 4. Pediatric drugs and formulations needed

Drug	Formulation and dose	Comments
Heat stable formulations of ritonavir and ritonavir-boosted PIs		
Lopinavir/ritonavir	Sprinkle, 40/10mg	Will be equivalent to 0.5ml of liquid
Ritonavir	Sprinkle or tablet (heat stable), 50mg Sprinkle (heat-stable), 25mg	Urgently needed for super-boosting when PIs need to be dosed with rifampicin
NRTI backbone combinations as FDCs		
Abacavir/lamivudine	Scored adult tablet, 300/150 mg	For children over 25kg
Tenofovir/lamivudine	Tablet, 75/75mg Scored tablet, 300/300mg	Approval of tenofovir in over 12 years in the United States; there is currently no FDC for this age group
Triple FDCs with NNRTI or boosted PI*		
Abacavir/lamivudine/nevirapine	Tablet, 60/30/50mg	Triple FDC to align with the dual FDC.
Abacavir/lamivudine/efavirenz	Copack	Dual FDC and efavirenz
Lamivudine/lopinavir/r/zidovudine	Copack	First line for NNRTI-exposed infants and children; second line for NNRTI-unexposed and older children
Abacavir/lamivudine/lopinavir/r	Copack	

Source: WHO Essential Medicines List
*It may not be possible to coformulate some combinations, as the individual drugs may have different dosing schedules. Dual blister packaging is preferred in these cases. Emtricitabine is considered interchangeable with lamivudine.

The working group also considered atazanavir, darunavir, etravirine, raltegravir, and tenofovir to be high priority. These drugs are currently approved for adolescents and adults but not for children. The development status and formulations of these drugs are described in Table 5.

As new antiretrovirals become approved, there will be more options for coformulations and copackaging.

Ones to Watch: The Innovator Pipeline

Since last year's report there have been a few changes:

- The pediatric investigational plan has begun with dolutegravir. (Shionogi/GSK/ViiV integrase inhibitor S/GSK-572).

- The cobicistat and Quad development plans were given a positive opinion by US and European Union (EU) regulatory agencies.

- The rilpivirine development plan is going ahead with the granule formulation.
- The dossier for the oral suspension of darunavir (boosted) for treatment-experienced children aged three to six years has been submitted to US and EU regulatory agencies.
- Raltegravir will be studied in neonates, first in a passive pharmacokinetic study and then dosed directly.

Nonnucleoside Reverse Transcriptase Inhibitors

Etravirine: The recommended dose per weight band for children and adolescents aged six to 17 will be based on 5.2mg/kg bid. The company will present 24-week data from the PIANO study in experienced adolescents this year; 48 weeks of the trial will be completed in the last patient later this year.[23]

An IMPAACT 1090 protocol is in development and the first patient is expected to enroll this year.

There is an upcoming submission for an indication for treatment experienced children and adolescents aged six to17 years and for the 25mg tablet.

Rilpivirine: The PAINT trial is of treatment-naive adolescents, aged 12 to18 years, weighing more than 32kg and receiving 25mg qd plus a background regimen.

TMC278-C220 is an open-label single-arm trial using the granule formulation, planned in children aged two to 12 years. This trial is taking a staggered approach and will study the drug in de-escalated age groups, down to two years of age.[24]

Nucleotide Reverse Transcriptase Inhibitor

Tenofovir DF: Although tenofovir was approved for adults in 2001 and is a preferred NRTI/nucleotide (Nt)RTI in international guidelines, pediatric development and approval has been slow. Bone toxicity and maturation concerns have been raised about using this drug in children.

The 300mg tablet is approved for adolescents 12 to18 years old weighing more than 35kg in the United States. However, recently the European Medicines Agency (EMA) did not approve an indication for this age group. The decision was based on the GS-US-104-0321 trial of treatment-experienced adolescents, in which tenofovir performed no better than placebo, but this study was underpowered, and on concerns about bone toxicity.

An additional study is ongoing to determine safety and efficacy in children below 12 years of age and under 35kg in weight, in which the 40mg/g oral powder is being evaluated.

A randomized open-label trial, 104-0352, is comparing switching stavudine or zidovudine to tenofovir versus continuing stavudine or zidovudine in virologically suppressed children. Children under 37kg receive the oral powder and those above this weight the 300mg tablet. This trial is ongoing.[25]

Protease Inhibitors

Atazanavir: The capsule formulation is approved for children in the United States aged six years and older who are treatment-naive and weigh 15kg or more and for treatment-experienced children weighing 25kg or more. In the EU it is approved for both treatment-naive and treatment-experienced children aged six years and older and weighing 15kg or more.

Younger children receiving atazanavir boosted with ritonavir are being studied in PACTG 1020A and PRINCE 1 and 2.[26,27]

Darunavir: The 75mg tablet is approved when boosted with ritonavir for children over six years of age. The dossier for the oral suspension for treatment-experienced children has been submitted for approval at the following doses: darunavir/ritonavir 25/3mg/kg bid for children weighing 10 to <15kg and darunavir/ritonavir 375/50mg bid for those weighing 15 to <20kg. There is a waiver for children under three years of age.

Integrase Inhibitors

Dolutegravir (S/GSK-572): 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 is in development.[28]

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

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

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

Raltegravir: IMPAACT 1060 is investigating this drug in de-escalated age bands. Data for children six to11 years of age and interim data for those two to five years of age, receiving the chewable formulation, have been presented. A dose of 6mg/kg (maximum 300mg) has been chosen. The chewable formulation has lower oral clearance than that of the adult tablet.[29]

Children under two years of age are now being enrolled in a study to determine the dose of the oral granule formulation.

IMPAACT P1097 is a washout (passive) pharmacokinetc and safety study. 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. This study is recruiting mothers already receiving raltegravir in pregnancy (the infants are not dosed directly). The infants will be sampled at intervals up to 30 to 36 hours after dosing.

After a review of pharmacokinetc and safety data from both trials the company is planning a study of infants born to HIV-positive mothers from immediately after the time of birth until their HIV status has been confirmed.

CCR5 receptor antagonists

Maraviroc: The A4001031 study is ongoing in children two to 12 years old who are infected with the CCR5-tropic virus (virus variants that use the CCR5 receptor for entry).[30]

Use of this drug requires a tropism assay, as it will not work for people with the CXCR4-tropic virus or in mixed-virus (CCR5/CXCR4) populations.

Further along the Pipeline, and One That Got Stuck

Other promising pipeline drugs, such as the prodrug of tenofovir, GS 7340, and the stavudine derivative festinavir, need to be studied in children as soon as sufficient adult data are obtained.

Over 12 years after efavirenz was approved in adults, there is finally a smattering of data for its use in children under three years of age—including TB-coinfected

infants—from IMPAACT P1070 and a couple of other investigator-led trials. Dosing difficulties with large variability remain. The bioavailability of the oral solution is less than 70% of that of the solid forms. High doses (i.e., large volumes of liquid) are needed to achieve adequate exposure in plasma.

This drug is important, as dosing with TB medications—specifically rifampin (rifampicin)—is complicated by boosted PIs and nevirapine. Whether there will be a suitable formulation of efavirenz with an indication for very young children remains to be seen.

TABLE 5. The Innovator Pipeline

Drug	Sponsor	Formulation	Comments
Atazanavir	BMS	Oral powder, 50mg sachet Capsule, 100mg, 150mg, 200mg, 300mg	Ongoing phase II PACTG 1020A and PRINCE 1&2, treatment-naive and treatment-experienced with or without ritonavir, from 3 months to 6 years
Darunavir	Tibotec/Johnson & Johnson	Oral suspension, 100mg/1mL	ARIEL phase II—filed with FDA/EMA for treatment-experienced, 3 to 6 years
Dolutegravir	Shionogi/ViiV	Older children: tablets, 10mg, 25mg, 50mg Younger children: to be decided.	Phase I and II IMPAACT P1093, from 6 weeks to 18 years
Elvitagravir/ cobicistat (booster)/Quad	Gilead	To be decided. Solid and liquid forms in development, separately and coformulated as Quad (solid tablet only)	183-0152 EVG, treatment-experienced 12 to 18 years; integrated plans for pediatric studies under discussion
Etravirine	Tibotec/Johnson & Johnson	Dispersible tablets, 25mg (scored), 100mg	Ongoing phase II PIANO, treatment-experienced, 6 to 17 years Phase I and II IMPAACT P1090, treatment-naive/treatment-experienced, 2 months to 6 years, planned
Maraviroc	Pfizer/ViiV	Oral suspension, 20mg/ml	Phase IV A4001031, treatment-experienced, CCR5-tropic, 2 to 12 years
Raltegravir	Merck	Chewable tablet, 25mg, 100mg Oral granules for suspension, 100mg sachet	Phase II IMPAACT 1066, 4 weeks to 18 years; IMPAACT P1097, neonates
Rilpivirine	Tibotec/Johnson & Johnson	Oral granules, 2.5mg base/g	Phase II, TMC278-C220, planned 0–12 years
Tenofovir DF	Gilead	Oral powder, 40mg/g 75mg tablet	Phase III, 104-0321 12 to 18 years; 104-0352, 2 to 12 years

What to Expect in the Future

Various ongoing discussions have anticipated how paediatric treatment guidelines might look in 2013 and 2016. This will depend on the approval status of some of the pipeline drugs and the results of ongoing trials.

When to Start?

2013: Universal treatment of all young children is anticipated to extend from up to 24 months to up to 36 months (or possibly five years) old.

2016: Universal treatment of all children less than five years old.

Children aged five or older share the criteria for treatment initiation with adults. This is currently at a CD4 count of 350 cells/mm^3 or lower, or at any CD4 count in the presence of active TB or hepatitis B.

The change will depend on the results of the INSIGHT START study 001. It is expected to mean starting at a CD4 count of 500 cells/mm^3 or lower, or a higher threshold.[31]

What to Start With?

2013: FDCs as much as possible and progressive phase-out of stavudine. Lopinavir/ritonavir–based treatment for all infants and children under three years of age regardless of NNRTI exposure.

2016: For all children under five years of age; either induction/maintenance of two NRTIs plus a boosted PI to achieve suppression and switch to rilpivirine to maintain suppression (this will depend on NEVEREST results) or two NNRTIs plus dolutegravir with or without switch.

What to Use Second-line?

2013: If lopinavir/ritonavir is used first, either NNRTI or darunavir (depending on approval—possibly etravirine or raltegravir).

If NNRTI is used first-line, boosted PI as second-line.

NRTIs will depend on the status of tenofovir and what was used first-line. Didanosine will continue to be an option although its phase-out is anticipated.

2016: Induction/maintenance first-line would allow for reuse of boosted PI or douletegravir for second-line, even if these were part of the initial (induction) regimen.

If integrase inhibitors are available, then second-line will probably be a boosted PI plus one of these; if not, then a boosted PI. Hopefully atazanavir and darunavir will be available in appropriate formulations.

If cobicistat is available it may offer an alternative to ritonavir as booster.

What to Use Third-line?

2013: Two or three regimens of integrase inhibitors (raltegravir), newer boosted PIs (darunavir) and newer NNRTIs (etravirine).

2016: Unclear, but etravirine may be less useful if ripivirine is given as maintenance.

The Drugs for Neglected Diseases Initiative

As a postscript to the pediatric pipeline, it deserves a mention that the Drugs for Neglected Diseases Initiative (DNDi) recently decided to add pediatric HIV to its portfolio. DNDi is a needs-driven, nonprofit, research and development organization founded in 2003 by partners including MSF and five public-sector research institutions. As the name suggests, the DNDi develops new treatments for the most neglected patients. DNDi's focus to date has been on visceral leishmaniases, Chagas disease, sleeping sickness (human African trypansomiasis, or HAT), and malaria. With its partners DNDi has introduced the first new treatment for HAT in 25 years and two inexpensive, field-adapted treatments for malaria.

DNDi was called on by various organizations, including MSF and UNITAID, to apply its expertise to the needs of children with HIV who are under three years old, NNRTI-exposed or -unexposed, and in need of first-line therapy, regardless of prior antiretroviral exposure.

They have come up with a target product profile that includes appropriate dosage forms usable across WHO weight bands, high genetic barriers to resistance, no cold chain needed, well tolerated, no lab monitoring required, and affordable. Any treatment would ideally be compatible with TB medicines.

We welcome DNDi's involvement and hope that it will usher in a promising new antiretroviral regimen—and at faster pace than we have become used to.

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HIV Point of Care Diagnostics Pipeline

BY POLLY CLAYDEN

Access to appropriate care and treatment is dependent on first diagnosing HIV and then managing the infection both on and off treatment.

For anyone over 18 months old, an initial HIV diagnosis is usually made using a rapid antibody test - of which there is quite an array of choices that are cheap, accurate, and easy to use within decentralized care.

CD4 tests are recommended for staging and monitoring the disease prior to initiating antiretroviral treatment—and for monitoring immune response to treatment, allowing opportunistic infection prophylaxis to be removed if higher CD4 counts are achieved—and viral load tests once treatment is started.

Because of passive transplacental transfer of maternal antibodies that can persist for up to 18 months antibody tests cannot be used for the accurate diagnosis of infants. So virological testing needs to be performed to determine an infant's HIV status and enable immediate initiation of antiretroviral therapy (ART).

Although there are currently many options available for CD4 and virological testing, they are expensive and require sophisticated, centralized laboratories and trained technicians. To improve access to diagnostics in resource-limited settings and to make them affordable, they must be delivered as close as possible to the patient. A recent technical report from UNITAID describes a "diagnostic landscape" with high volume testing performed in centralized facilities ("super labs") where feasible, and, most importantly, a drive towards decentralized point of care (POC) testing in harder to reach populations.[1]

This chapter looks at the latter and describes promising POC technologies in the pipeline for CD4, viral load and early infant diagnosis (EID). These tests may be commercially available within the next couple of years. Many of the test sponsors appear to believe that their products will launch commercially next year. If their predictions come true then 2012 will be a bumper year for HIV POC diagnostics. The authors cannot guarantee that this bonanza will occur in 2012.

DIAGNOSTIC TESTS

CD4

CD4 tests determine the number or percentage of CD4 T cells in a mm^3 of blood.

Flow cytometry is the gold standard technique for CD4 testing. It is a technique for counting CD4 cells by suspending them in a stream of liquid and passing them by an electronic detector.

The machines used to perform these tests are big and expensive, use complex systems of lenses, lasers and electronics, and require an uninterrupted supply of electricity and highly trained technicians.

PCR

Polymerase Chain Reaction (PCR) tests detect the genetic material of HIV (rather than antibodies). Extracting and amplifying the genetic material of HIV and then detecting it with a PCR test is called nucleic-acid amplification testing or NAT. NAT tests are either, RNA PCR (viral load) or DNA PCR (which detects HIV when integrated into the host cell's DNA) tests.

DNA-PCR testing is most commonly used for EID. Although DNA-PCR has been used in resource-limited settings, its long turnaround time contributes to infant loss-to-follow-up and loss of benefit of immediate initiation of treatment. These tests do not provide measurements like RNA-PCR, but just detect the presence of the virus and give a "yes" or "no". Currently, no POC DNA-PCR tests are available for infants.

p24

The p24 protein is the antigen that most commonly provokes an antibody response to HIV. Early in HIV infection, p24 is produced in quantity and can be detected in the blood. It falls to low levels as the infection becomes established.

p24 antigen tests are not usually used for general HIV diagnosis, as they have a very low sensitivity and they only work before antibodies are produced in the period immediately after HIV infection. But p24 tests could be useful for EID.

In order for a diagnostic test to be useful within a decentralized setting it should meet the WHO ASSURED criteria for the ideal rapid test, which is as follows:

A = affordable
S = sensitive
S = specific
U = user friendly (simple to perform in a few steps with minimal training)
R = robust and rapid (results available in less than 30 minutes)
E = equipment free
D = deliverable to those who need the test

CD4 Tests

The CD4 Initiative, based at Imperial College in London, was set up in 2005 to develop simple, instrument-free CD4 point of care tests designed specifically for rural areas in resource-limited settings.[2]

They began with a target product profile with a set of specifications that elaborate on the ASSURED criteria.

- Simple and robust
- Semi-quantitative, minimum cut off of 250 cells/mm^3
- Stable at 40ºC for 12 months
- Quality assurance material to check correct functioning of test
- Use of finger-prick blood/other non-venous blood sample
- Simple to perform, few steps and <2 hours training required
- <30 minutes from patient to result
- Simple read out
- All-in-one kit
- 25 tests performed/person/day
- Target price around $2 per test
- Customer capital outlay (if any) <$1,000
- Safe solution for infectious waste materials

In partnership with Zyomyx they have developed a fully quantative CD4 counter, that can be read visually without an electronic reader, much like a thermometer. It consists of a disposable cartridge with a mechanical spinner that requires no power supply. The test can measure an absolute CD4 count without complex instruments. Clinical trials are expected in 2011. If the results are positive, the test could begin to become available by 2012, according to Zyomyx.[3]

The Burnet Institute—who also worked on their prototype within the CD4 Initiative—is continuing to develop a rapid CD4 test in collaboration with the Rush University Medical Center and Duke University.[4]

This test is semi-quantative and will give a read out showing whether someone's CD4 count is above or below a predetermined threshold—e.g., 350 cells/mm^3. The user then can make a treat/don't treat decision. Burnet is developing a reader for the device in collaboration with Axxin Ltd.

Clinical trials are planned in 2011 in the United States and Malawi. The further development and the launch of this test will depend on trial results and project funding.

Daktari Diagnostics is in late stage development of a portable CD4 cell counter. The device is a portable battery run instrument. Each CD4 test consists of a disposable plastic card, which is inserted into the instrument. The test measures absolute CD4 count.[5]

Validation studies in four African countries are expected to be underway this year. Follow-on studies in additional countries are also planned. The commercial launch is expected at the end of 2011.

MBio Diagnostics is developing a system that uses disposable cartridges and a simple reader instrument. It provides an absolute CD4 count.[6]

Field-testing in southern Africa is scheduled for later this year.

TABLE 1: CD4 point of care test pipeline

Test	Turnaround time/ capacity	Sample needed	Cost test/ instrument*	Power	Environment	Training (layperson)
Zyomyx CD4 counter	10 minutes 40 samples per day	100 uL finger stick blood	$6-7 $100	None	TBD	Less than 30 minutes
Burnet Institute CD4 counter	20 minutes 8-10 tests per hour (running cartridges in parallel)	10 QL finger stick blood; can also use venous blood	TBD	Battery	TBD	Less than 120 minutes
DaktariTM CD4 Counter	8 minutes 40-50 samples per day	20 QL finger stick blood applied to cartridge	$8 $800	AC, on board long life rechargeable battery	Temperature 40 to 370	Less than 90 minutes
M Bio CD4 system	20 minutes 8-10 tests per hour	10 QL finger stick blood; can also use venous blood	TBD	Battery	TBD	Less than 90 minutes

*Estimated cost

Viral Load

The SAMBA (simple amplification based assay), is currently being developed by the Diagnostics Development Unit at the University of Cambridge.[7]

They are developing two tests, a semi quantative test for monitoring ART and a qualitative test for EID. The tests use isothermal amplification and visual detection by dipstick. SAMBA is being field tested by MSF in Malawi.[8]

The Liat TM Analyser, manufactured by IQuum, POC HIV assay is a real time, battery operated, small, portable, PCR kit. Blood is collected in a tube and inserted into the analyzer. Results are quantitative.

Clinical trials are scheduled for 2011 with the potential for launch in 2012.[9]

Alere NAT system is a generic platform designed to detect various nucleic acids. The first test—anticipated to be commercially launched next year—is a real time detection method for measuring quantative HIV RNA. The sample—which can be from finger-stick, whole blood, or plasma—is applied directly onto the disposable cartridge, which is processed by a compact, battery driven instrument.[10]

TABLE 2: Viral load point of care test pipeline

Test	Turnaround time/ capacity	Sample needed	Cost test/ instrument*	Power	Environment	Training (layperson)
SAMBA	60 minutes 4 samples per run	200mL plasma or 100 QL blood	TBD $2500 to $5000	AC or battery	N/A	Minimal
LiatTM Analyser	30 to 55 minutes 8 to 15 samples per day (depending on limit of detection)	200mL plasma or 10-50 QL of finger stick blood	TBD	AC or battery	Operating Temperature 15o to 30o C (59o to 86o F)	One hour
Alere	30 to 60 minutes	25 QL finger stick	TBD	On board rechargeable battery	Operating Temperature: 15o to 40o C (59o to 104o F) Humidity: < 90% relative humidity Maximum altitude: N/A (permissible atmospheric pressure: 850 to 1100 hPa)	Less than 90 minutes

*Estimated cost

Early Infant Diagnosis

Virological testing or ultrasensitive p24 antigen testing should be used for EID. It is possible to use qualitative HIV RNA assays, as described above, as an alternative to HIV DNA. The SAMBA system is developing a test especially for this purpose.

North Western Global Health Foundation (NWGHF) is developing an HIV DNA-PCR test which is on hold—is not yet ready for field-testing—while the group focuses on a POC p24 test.[11]

Both Micronics and BioHelix have DNA tests which appear to be in the proof of concept stage and are not ready for field-testing yet either.

The NWGHF p24 antigen rapid test consists of a plasma separator, reaction tube, reaction buffer, and rapid test strip. It is small, battery operated, and expected to be inexpensive. It has demonstrated about 95% sensitivity and 99% specificity.[12]

Clinical and field trials are expected to start this year and it should be available in 2012.

TABLE 3: p24 test for EID pipeline

Test	Turnaround time/capacity	Sample needed	Cost test/ instrument*	Power	Environment	Training (layperson)
NWGF p24 lateral flow assay	30 minutes 16 samples per day	75mL heel stick blood	$10 $150	Battery	TBD	Minimal

*Estimated cost

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Patents and the Pipeline: Is Access Under Threat?

BY JONATHAN BERGER

Introduction

Access to the pipeline, particularly in developing countries that are home to a disproportionate share of the global population of people with HIV, will by no means be guaranteed. Numerous barriers may stand in the way of timely access, including but not limited to slow drug registration processes, inefficient domestic procurement policies, and problematic supply chain management practices. But, as was the case with access to treatment in the developing world in the late 1990s and early 2000s,[1] the single biggest barrier to access may indeed be the high prices of new drugs.

Central to the affordability of medicines is the existence of adequate generic competition. This, in turn, is dependent on a number of intellectual property–related factors, including the patent status of the drug in countries with significant generic pharmaceutical manufacturing capacity (in particular India), the patent status of the drug in the country in whose market generic competition is required, and/or the licensing policy of the relevant patent holder. Some detail on the licensing policies of companies with products in the pipeline is provided below. But before that, this section considers the global context that affects the nature of domestic patent laws.

Threats to countries' ability to manufacture and supply affordable drugs

Since amending its laws in 2005 to ensure compliance with the World Trade Organization (WTO) Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS),[2] India has been subjected to numerous threats to its ability to manufacture and supply affordable generic finished products and active pharmaceutical ingredients (APIs). The rapidly changing nature of the Indian generics industry has been accompanied by the rising grant of product patents, with new products for the first time in decades not being subjected to generic competition; this includes many new-generation antiretroviral (ARV) medicines.

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While India took great care in ensuring that its amended laws take advantage of a range of public health safeguards and flexibilities in TRIPS, something that many developing countries such as South Africa have thus far failed to do, the post-TRIPS era is one in which access has unquestionably been curtailed. Put differently, an international patent regime that does not require minimum levels of patent protection for all pharmaceutical products would mean more people having access. But instead of a move in this direction, "the policy space to produce or import generic versions of patented medicines [within the context of TRIPS] is shrinking in some developing countries." As 't Hoen et al. explain:

> Stringent intellectual property provisions exceeding TRIPS requirements ("TRIPS-plus") have been negotiated into free trade agreements between industrialized and developing countries, and/or investment and WTO accession agreements. Measures, such as patent term extensions, data exclusivity, patent-registration linkage and border enforcement requirements, can all delay access to generics by lengthening, strengthening or broadening monopolies on medicines. In addition, some agreements contain measures that confuse legitimate generics with counterfeit medicines; such policies can undermine public health by restricting access to affordable, quality-assured generic medicines. Countries that enter into agreements that undermine access to medicines are arguably violating their international human rights obligations.[3]

In recent years and months, India has been under pressure from the European Union (EU) to conclude a free trade agreement (FTA) that, if adopted in the form proposed by the EU, would substantially undermine India's already-constrained ability to produce affordable medicines.[4] At the June 2011 UN High-Level Meeting on HIV and AIDS, India formally announced that it will not accept data exclusivity—a provision that has the potential to limit access to medicines, and that is not required by TRIPS—as part of the FTA it is currently negotiating with the EU.

But other problematic provisions that threaten access remain on the EU's negotiating agenda.

According to Médecins Sans Frontières (MSF), "Europe is still pushing provisions on the enforcement of intellectual property that are of great concern for procurers and suppliers of medicines . . . [that put them] at risk of litigation or court orders that prevent [them] from delivering medicines to patients". In addition, the EU is also proposing an investment chapter that "includes measures to protect the commercial interests of foreign companies investing in India . . . [by giving them] the right to bypass Indian courts and sue the Indian government in secret international arbitration panels that do not balance public health against private profit."[5]

Licensing policies

While the global context and resultant domestic patent laws are central to determining whether medicines are affordable, so too is the conduct of exclusive rights holders (whether patent holders or exclusive licensees) and their approach to licensing. One option available to companies is the Medicines Patent Pool,[6] which was established in the late 2000s and is expected to work as follows:[7]

> Patent holders will make licenses available through the Pool that will allow others to produce low-cost generic versions of patented ARVs for use in developing countries. It will be important that the licenses cover as many developing countries as possible, both to maximize public health benefit and to ensure economies of scale in generic drug production. The licenses are also intended to facilitate the development of FDCs and other formulations adapted for use in resource-poor settings, such as special formulations for treating children, by ensuring that patents do not block generic companies or product development initiatives from carrying out follow-on R&D.
>
> Companies that receive licenses from the Pool will pay royalties on their sales to the patent holders. The Pool will be a systematic and predictable way of making voluntary licences available, offering legal certainty to all parties involved. No change in international or national law is required for the Pool to work; what is required is a change in mindset from the patent holders, without whose collaboration this initiative cannot succeed. In other words, the Patent Pool will work only if patent holders are willing to collaborate to make their intellectual property available to the Pool.

On 12 July 2011, the Medicines Patent Pool announced its first agreement with a pharmaceutical company – Gilead Sciences.[8] Whilst the agreement will result in expanded access to the company's products, including those currently in the pipeline, numerous of its provisions have drawn criticism: for example, the agreement excludes a number of developing countries with high HIV burdens and places limits on API sourcing. Given the voluntary nature of the Pool, it is unsurprising that the agreement does not go far enough.

A second option is adopting access-friendly patent enforcement and/or licensing policies. In the next section we consider whether companies with key products in the pipeline have addressed this issue, and if so, how. These companies are:

- Abbott Laboratories;
- Boehringer Ingelheim (BI);
- Bristol-Myers Squibb (BMS);
- Gilead Sciences;
- Merck & Co.;
- ViiV Healthcare;
- Tibotec; and
- Tobira Therapeutics.

Abbott Laboratories

Abbott has consistently refused to license any company to produce generic versions of its fixed-dose combination lopinavir/ritonavir (LPV/r); it is, however, prepared not to enforce its patent on the soft-gel formulation of ritonavir (RTV) in South Africa. [9] That said, there is currently no patent barrier to the production of generic LPV/r or RTV in India;[10] importation from India depends solely on the patent status of the relevant product in the importing country and whether a compulsory licence for importation has been issued in that country (in the event that the relevant product is indeed under patent protection).

BI

According to its policy paper on HIV/AIDS, BI does not enforce its patents on nevirapine and tipranavir in the following countries: low-income countries as defined by the World Bank;[11] least-developed countries (LDCs) as defined by the United Nations Development Programme;[12] and all African countries that are not classified as low-income or LDCs.

This policy, which applies to immediate-release and extended-release versions of nevirapine, means that companies in eligible countries—without the need for any legislative or administrative action—may lawfully manufacture generic products. They may also export products to and/or import them from other eligible countries.

Of concern, however, is that the policy does not cover middle-income countries outside of sub-Saharan Africa, including those such as Brazil, China, India, and Thailand with significant generic pharmaceutical manufacturing capacity. This limits the ability of the eligible countries to import generic finished products and APIs, with manufacturers based in countries such as Kenya and South Africa being almost completely reliant on the importation of APIs.

BMS

BMS does not enforce the exclusive marketing rights it holds on didanosine (ddI), stavudine (d4T) and atazanavir (ATV) in sub-Saharan Africa. Since 2001, it has entered into 11 "immunity-from-suit" agreements in respect of ddI and d4T; it has committed to entering into similar agreements with requesting companies in respect of ATV. In 2006, BMS granted royalty-free licenses to, and entered into technology transfer agreements with, two companies—one in South Africa and the other in India— regarding the production of generic ATV and its sale in sub-Saharan Africa.

On the one hand, this approach is an improvement on BI's: it has resulted in the licensing of an Indian generics company—a member of the Clinton Health Access Initiative (CHAI) consortium—with significant manufacturing capacity in respect of quality finished products and APIs. On the other, the limitation on the number of licensees has implications for competition and pricing; the best international prices for ATV still remain too high.

BMS's publicly stated position on intellectual property suggests that the company is open to following this approach in respect of pipeline products such as BMS-663068.

Gilead Sciences

Following the introduction in 2005 of patent protection on pharmaceutical products in India, Gilead began to enter into non-exclusive licensing agreements with a range of generics companies for the manufacture and sale of tenofovir disoproxil fumarate (TDF) and the fixed-dose combination (FDC) of TDF and emtricitabine (FTC).[13] These agreements, which were concluded prior to any final decisions of the authorities in India regarding the relevant patent applications, apply both to finished products and APIs. As of April 2011, Gilead had licensed 14 companies: 13 in India and one in South Africa.[14]

The agreements permit the licensees to manufacture generic TDF and TDF/FTC in India and to sell finished products in India and an additional 94 countries,[15] including a range of middle-income countries such as Thailand, Moldova, and various states in Central America and the Caribbean. Licensees are entitled to buy APIs from—and sell them to—each other, as well as to obtain APIs from Gilead's own supplier. All licensees are required to pay Gilead a five percent royalty on the sale of finished products.

The agreement between Gilead and the Medicines Patent Pool, details of which were released on 12 July 2011, follows a similar approach in respect of the company's pipeline products: elvitegravir (EVG); cobicistat (COBI); and the FDC of

TDF/FTC/EVG/COBI ("Quad"). Under the terms of the agreement, Indian generics companies will be licensed by the Pool to produce and sell APIs (to each other) and finished products (to a list of countries). Licensees may also sell to countries in which compulsory licences for import have been issued.

In addition to the 95 countries already covered by earlier agreements, licensees will be able to sell finished TDF and TDF/FTC products in 16 more countries, including 7 in the Caribbean and Latin America, 4 in Eastern Europe and Central Asia, and 4 in the Pacific. But the geographic scope of the pipeline products is more restricted: 12 of the 111 countries are excluded from the COBI licence, with 3 of these countries also being excluded from the EVG and Quad licences.

Merck & Co.

Merck does not appear to have any coherent approach to licensing. That said, the company has—in response to legal action—licensed numerous companies for the production of generic efavirenz (EFV) products in, and/or the importation of EFV products into, South Africa. In addition, government-issued compulsory licenses in Thailand and Brazil have paved the way for the introduction of affordable generic EFV products. In India, there are no product patents on the drug and consequently at least six Indian companies are producing it currently.[16, 17]

According to the MSF Access Campaign, Merck and the Institute for Research in Molecular Biology (IRBM)[18] applied for patents on raltegravir (RAL) in a number of developing countries with generic drug manufacturing capacity, such as Brazil, China, India, and South Africa. IRBM was granted a patent on RAL in India in December 2007, which will expire only in 2022. Unless and until Merck is effectively compelled to license RAL to manufacturers in India and/or other developing countries with generic drug manufacturing capacity, access to RAL products will remain out of reach for the majority of those living with HIV in developing countries.

ViiV Healthcare

ViiV's voluntary licensing policy, in terms of which royalty-free licences are offered to generics companies to manufacture and sell all its current products and those in the pipeline, covers 69 countries: all LDCs, low-income countries, and sub-Saharan African countries. This policy also extends to the integrase inhibitor dolutegravir, currently being developed jointly by ViiV and Shionogi. As is the case with the BI policy, ViiV's does not cover middle-income countries outside of sub-Saharan Africa, including those with significant generic pharmaceutical manufacturing capacity; this limits the ability of the listed countries to import generic finished products and APIs.

Tibotec

Tibotec's Global Access Programme (GAP)—which first addressed access to darunavir (DRV) and etravirine (ETV)—was initially focused on sub-Saharan Africa and LDCs. This has been expanded with rilpivirine (RLV): prior to the drug's licensure in the United States, Tibotec granted multiple non-exclusive licences to generics companies (including two in India and one in South Africa) to manufacture, market, and distribute finished products. The Indian companies—of which there are now four—have the right to market in sub-Saharan Africa, LDCs, and India; South Africa's Aspen is limited to sub-Saharan Africa.

The agreements extend to the development, manufacturing, and distribution of two FDCs containing RPV: TDF/3TC/RPV and TDF/FTC/RPV. No agreement has yet been reached in respect of the relevant API: generic production of the single agent and/or the FDCs will require the purchase of the RPV API from Tibotec.

Tobira Therapeutics

Tobira is a private company that was founded only in 2006. On 22 June 2011, it announced that it had started a phase IIb clinical trial for the CCR5/CCR2 inhibitor cenicriviroc (TBR-652); the drug, therefore, still has two to three years of clinical development left to assess safety and efficacy in support of regulatory authority approval. Tobira has indicated that its access policies will be determined only after substantial completion of this clinical work.

References

1. See Ellen 't Hoen et al., "Driving a decade of change: HIV/AIDS, patents and access to medicines for all", Journal of the International AIDS Society. 2011 March 27;14:15. Available at http://www.jiasociety.org/content/14/1/15.

2. For more information on the impact of TRIPS on access to medicines, see 't Hoen et al., ibid.

3. Ibid.

4. India is not alone. Other countries—such as South Africa and its partners in the Southern African Customs Union, Mozambique and Angola—may have faced similar pressures. In this regard, see http://www.section27.org.za/2011/03/16/proposed-economic-partnership-agreement-with-the-eu-raises-concerns-about-access-to-medicines.

5. See http://www.msfaccess.org/media-room/press-releases/press-release-detail/?tx_ttnews[tt_news]=1700&cHash=2f6721d292.

6. See http://www.medicinespatentpool.org/.

7. Numerous companies are currently in negotiations with the Patent Pool. For further detail in this regard, see http://www.medicinespatentpool.org/LICENSING/Company-Engagement.

8. See International Treatment Preparedness Coalition and Initiative for Medicines, Access & Knowledge Briefing Paper, "The Implications of the Medicines Patent Pool and Gilead Licenses on Access to Treatment", accessed 11 August 2011 at http://www.i-mak.org/publications/. But also see Krista Cox, "Medicines Patent Pool agreement with Gilead contains flexibilities including termination provisions and severability of licenses", accessed 11 August 2011 at http://www.keionline.org/node/1192

9. This waiver of rights applies only to the production of the soft-gel capsule version of RTV for sale and use in South Africa.

10. According to the MSF Access Campaign, Abbott applied for several patents on the solid dosage formulation and polymorphic forms of LPV/r and its constituent parts. A number of these applications were opposed by civil society organizations and generics companies. Opposition to the LPV/r soft-gel formulation patent application resulted in it being withdrawn; on 30 December 2010, the Indian Patent Office decided that LPV/r does not merit a patent under Indian law. For further information in this regard, see http://utw.msfaccess.org/drugs/lopinavir-ritonavir and http://msf-utw.tumblr.com/post/2624553835/india-rejects-patent-for-aids-drug-lopinavir-ritonavir.

11. See http://data.worldbank.org/about/country-classifications/country-and-lending-groups#Low_income.

12. See http://www.un.org/wcm/content/site/ldc/home/Background/quick_facts.

13. The history of Gilead's Global Access Program (GAP) is available at http://www.gilead.com/pdf/GAPHistory.pdf.

14. Gilead's initial agreement with South Africa's Aspen Pharmacare was for the production and distribution of co-branded Viread and Truvada in Africa, using APIs from Gilead's supplier. In November 2007, Gilead and Aspen entered into a full licensing agreement with terms and conditions similar to those granted to the Indian licensees.

15. The full list of companies is available at http://www.gilead.com/access_partnerships#distribution.

16. MSF 2011. Untangling the web of antiretroviral price reductions. 2011 edition. Accessed 23 June 2011 at http://utw.msfaccess.org/drugs/efavirenz.

17. According to the MSF Access Campaign, there are concerns regarding the potential impact of a patent for the process of preparing form 1 of crystalline EFV that was granted in India in June 2005—it appears to protect a key process for manufacturing the drug. Opposition to that patent is ongoing.

18. IRBM, which is based in Pomezia in Italy, is one of Merck's research sites.

Preventive Technologies, Immune-Based and Gene Therapies, and Research Towards A Cure

BY RICHARD JEFFERYS

The phrase "product pipeline" typically conjures up the notion of multiple experimental candidates incrementally advancing along a pre-plumbed path toward licensure and widespread availability. But for most of the approaches described in this section of the report, the route toward a pharmacy shelf is far more convoluted and uncertain. Few large pharmaceutical companies are involved in the development of the candidates listed here; the majority are collaborative efforts between small biotech firms, academic researchers, non-profits, and government funders. And even those with the support of a major manufacturer can face unique obstacles related to their novelty, because there are as yet no approved precedents in any of these realms.

The current state of the biomedical prevention pipeline offers illustrative examples. After decades of disappointment and frustration, the past few years have seen low but statistically significant efficacy reported for each of the main approaches: vaccines, microbicides, and, most recently, preexposure prophylaxis (PrEP). The vaccine trial, named RV144, involved an ALVAC canarypox vector made by Sanofi-Pasteur combined with an envelope protein booster shot, AIDSVAX. While Sanofi-Pasteur remains committed to following up on the marginal degree of protection (31.2%) observed among recipients of the regimen (Rerks-Ngarm 2009), the company that made AIDSVAX, VaxGen, ceased to exist several years ago after the product failed to show efficacy given alone. Attempts to duplicate and improve upon the results have thus been slowed by the need to secure a new manufacturer for the envelope protein boost.

Greater success was reported last year with a microbicide consisting of a 1% vaginal gel form of the antiretroviral drug tenofovir (Viread), which demonstrated 39% protective efficacy in the CAPRISA 004 trial in South Africa (Abdool Karim 2010). However, the next steps toward licensure have proven surprisingly slippery. The U.S. Food and Drug Administration (FDA) has indicated that at least one more confirmatory trial (in addition to an ongoing study called VOICE) will be sufficient for them to consider the product for approval, but securing the relatively small amount of funding necessary for the new efficacy evaluation proved difficult and time-consuming. The trial,

FACTS 001, is now expected to get underway in August 2011. The maker of Viread, Gilead Sciences, has licensed the gel form to the nonprofit organization CONRAD, so the development of the microbicide also represents a test case for the viability of nonprofit manufacturing and marketing.

Among the most significant biomedical prevention news since the last TAG pipeline report in 2010 was the announcement of the long-awaited first efficacy results of PrEP in HIV negative gay men and transsexual women at high risk of infection (Grant 2010). The iPrEx study found that individuals assigned to receive Truvada (a pill combining two antiretroviral drugs, tenofovir and emtricitabine) experienced a 44% reduction in risk of HIV infection, with additional analyses indicating that protection was significantly better among participants who closely adhered to the regimen. While Gilead donated Truvada for this and other PrEP studies, it was not otherwise involved and it was unclear whether the company would pursue a prevention indication for the drug. After the iPrEx findings were announced, Gilead expressed its intent to submit the data to FDA for consideration, which provoked a vociferous and at times acrimonious debate regarding whether such a filing would be appropriate or premature. Subsequently, the picture was further complicated when news emerged that a trial of Truvada as PrEP in women was being stopped after an interim analysis found it would be unable to show efficacy. A broad lesson from all these biomedical prevention developments is that an approach can get tantalizing close to the end of the pipeline, yet still face significant impediments to actually emerging from it.

Immune-based therapies (IBTs) and gene therapies for HIV have long been entrenched in a distant corner of the research field. This is partly due to uncertainties about mechanisms of action and how best to define and measure success, particularly in light of the dramatically beneficial effects of HIV suppression with antiretroviral drugs. But resurgent interest in curing HIV infection is now helping to move these types of approaches toward the mainstream. In particular, the widely reported case of Timothy Brown, who has remained off antiretroviral therapy and free of detectable HIV for four years and counting after a complex series of high-risk treatments for cancer—including stem cell transplants from a donor lacking the CCR5 receptor—is viewed as a compelling proof of concept that a cure for chronic HIV infection is possible (Allers 2011). The goals for potentially curative therapies are relatively straightforward: either eradicate HIV completely (to the extent that this can be verified with current testing technologies) or induce long-term control of the virus in the absence of ongoing treatment (referred to as a functional cure). In addition to IBTs and gene therapies, cure research includes treatments—most notably histone deacetylase (HDAC) inhibitors—that aim to awaken the latent HIV that otherwise can persist for life in dormant form, integrated into the host cell's DNA, invisible to the immune system, yet subject to reactivation by immune stimuli or to renewed replication when the resting infected cell divides.

Another potential role for IBTs and gene therapies is addressing the immune system dysfunction that can persist in some individuals despite HIV suppression. Examples include inadequate CD4 T cell recovery, elevated levels of immune activation and inflammation, and an accelerated aging of the immune system called immunosenescence. Studies have linked all of these phenomena to an increased risk of ill health (Marin 2009; Tan 2008; Tien 2010; Deeks 2011), suggesting that an IBT and/or gene therapy capable of addressing them could conceivably offer clinical benefits.

Results from three groundbreaking biomedical prevention trials were presented at the International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention in July 2011. HIV Prevention Trials Network trial 052 (HPTN 052) was a randomized comparison of the effects of earlier initiation of antiretroviral therapy (at CD4 T-cell counts of between 350 and 550 vs. <350) on sexual transmission of HIV among serodiscordant couples. The trial was stopped ahead of schedule by the Data Safety Monitoring Board (DSMB) after an interim analysis revealed that earlier treatment reduced HIV transmission by 96% and also significantly reduced the incidence of extrapulmonary TB. The results have now been published in the New England Journal of Medicine and are available free online (Cohen 2011).

Results also became available from two independent clinical trials evaluating the efficacy of PrEP among heterosexuals at risk of HIV infection. Initially announced by press release, details were presented at the IAS conference in July 2011. In both cases, a statistically significant reduction in risk of HIV acquisition was documented in the trial participants receiving daily PrEP (consisting of the antiretroviral drugs Viread or Truvada) compared to placebo. The larger of the trials, named Partners PrEP, enrolled 4,758 HIV-serodiscordant couples in Kenya and Uganda and randomized the HIV-negative partners to receive either Viread, Truvada, or placebo. A total of 78 HIV infections occurred: 47 in the placebo group, 18 in the Viread group, and 13 in the Truvada group. This equated to a 73% reduction in risk of HIV acquisition for those assigned to Truvada and a 62% reduction among those in the Viread arm (Baeten 2011).

The second trial (called TDF2) was conducted by the U.S. Centers for Disease Control (CDC) in Botswana. The population was not couples in this case, but 1,200 sexually active men and women aged 18-39 (54.7% male/45.3% female) in Gaborone and Francistown. Participants were randomized to receive either Truvada or placebo. There were a total of 33 HIV infections during follow-up: 9 among the 601 individuals in the Truvada group and 24 among those assigned to placebo. The reduction in risk of HIV acquisition was 62.6%, a statistically significant result. In an analysis restricted to participants known to have a supply of Truvada (i.e. those who had not missed a study visit at which 30-day supplies of drug were dispensed), efficacy was reported to be 77.9%. Similar efficacy was observed in both men and women. The side effects reported more often in the Truvada arm compared to placebo were nausea, vomiting, and dizziness (Thigpen 2011).

The results of Partners PrEP and TDF2 contrast with the trial of Truvada as PrEP in women (the FEM-PrEP study), which was unable to show efficacy due to similar HIV infection rates in the active and placebo arms. The reason for the divergent outcome of FEM-PrEP remains to be fully elucidated, but could relate to differences in adherence and/or an enhanced risk of HIV acquisition associated with the use of hormonal contraceptives (Heffron 2011).

Taken together with prior results from iPrEx and CAPRISA 004, the new findings underscore the efficacy of antiretrovirals in preventing HIV infection. Along with the demonstrated effectiveness of circumcision in reducing risk of HIV acquisition in men (Weiss 2010), there is clearly potential to greatly reduce HIV incidence if the political will and funding support can be mustered to appropriately implement the tools now available.

TABLE 1. HIV Vaccines Pipeline 2011

Product	Type	Manufacturer/Sponsor	Status
ALVAC 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/US HIV Military HIV Research Program (USMHRP)/ National Institute of Allergy and Infectious Diseases (NIAID)	Phase IIb
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	GenVec/Vical/NIH Vaccine Research Center (VRC)/NIAID	HVTN 505
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
ISS P-001	Recombinant Tat protein from HIV-1 clade B	Istituto Superiore di Sanità, Rome/Excell	Phase IIA
LIPO-5	Five lipopeptides containing CTL epitopes (from Gag, Pol and Nef proteins)	Agence Nationale de Recherche sur le Sida et le hepatitis (ANRS)	Phase II
HIVIS 03 DNA-MVA prime-boost HIV-1 vaccine candidate	Prime: HIVIS DNA including env (A, B, C), gag (A, B), reverse transcriptase (B), rev (B) genes Boost: MVA-CMDR including env (E), gag (A), pol (E) genes	Vecura/Karolinska Institute/Swedish Institute for Infectious Disease Control (SMI)/ USMHRP	Phase I/II
DNA-C + NYVAC-C	Prime: DNA vaccine including clade C env, gag, pol, nef genes Boost: NYVAC-C attenuated vaccinia vector including clade C env, gag, pol, nef genes	GENEART/Sanofi Pasteur/ Collaboration for AIDS Vaccine Discovery (CAVD)	Phase I/II
PolyEnv1 EnvDNA	Vaccinia viruses including 23 different env genes and DNA vaccine with multiple env genes	St. Jude Children's Research Hospital	Phase I

VICHREPOL	Chimeric recombinant protein comprised of C-terminal p17, full p24, and immunoreactive fragment of gp41 with polyoxidonium adjuvant	Moscow Institute of Immunology/ Russian Federation Ministry of Education and Science	Phase II
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 TrigridTM electroporation	Ichor Medical Systems/Aaron Diamond AIDS Research Center/ International AIDS Vaccine Initiative (IAVI)	Phase I
GSK HIV vaccine 732461	Gag, Pol, and Nef proteins in proprietary adjuvant	GlaxoSmithKline	Phase I Prime-boost phase I w/ Ad35-GRIN
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 w/ 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 w/ Ad35-ENVA
Ad35-ENVA	Prototype adenovirus serotype 35 vector including the HIV-1 subtype A env gene	Crucell/IAVI/NIAID/Beth Israel Deaconess Medical Center/Ragon Institute of MGH, MIT and Harvard	Prime-boost phase I w/ Ad26.ENVA.01
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
rAd35 VRC-HIVADV027-00-VP	Adenovirus serotype 35 vector	VRC/NIAID	Phase I
ADVAX + TBC-M4	Prime: DNA vaccine including env, gag, nef-tat and pol genes from HIV-1 subtype C Boost: MVA vector including env, gag, tat-rev, and nef-reverse transcriptase genes from HIV-1 subtype C	Indian Council of Medical Research/ IAVI/Aaron Diamond AIDS Research Center	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

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)
MYM-V101	Virosome-based vaccine designed to induce mucosal IgA antibody responses to HIV-1 Env	Mymetics Corporation	Phase I/II
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
MV1-F4-CT1	Recombinant measles vaccine vector including HIV I Clade B Gag, Pol & Nef	Institut Pasteur	Phase I
rVSVIN HIV-1 gag	Attenuated réplication-competent recombinant vesicular stomatitis virus (rVSV) vector including HIV-1 Gag protein	Profectus Biosciences, HVTN	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
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
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
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

Spurred by the borderline but statistically significant protection observed in the RV144 trial of ALVAC/AIDSVAX, HIV vaccine research continues to move ahead on multiple fronts.

Identifying Correlates of Protection in RV144

Many scientists are engaged in the search for immunological markers that might have been linked to protection against HIV in the RV144 trial. Identification of such "correlates of protection" is one of the Holy Grails of vaccine research and currently, according to Jerome Kim from the US HIV Military HIV Research Program, 35 investigators from 20 institutions are working on 32 different assays that could potentially be used to analyze RV144 samples (Kim 2011). Data from this work should start to become available toward the end of 2011. In the meantime, Kim and colleagues have unveiled some of their results hinting that CD4 T cells targeting the V2 region of the HIV envelope could have played a role in the trial outcome (Currier 2011).

Replicating and Extending the RV144 Results

While the vaccine field has been buoyed by RV144, there remains a deflating possibility that the observed evidence of protection was not a consequence of immunization, but simply a result of chance. A recently published statistical reevaluation of the efficacy result argues there is a 22% or greater probability it was spurious, which the authors note is "an inference that reflects greater uncertainty than has much of the discussion about this trial" (Gilbert 2011). This uncertainty emphasizes the importance of efforts to try and replicate and extend the RV144 findings.

The HIV Vaccine Trials Network (HVTN) has published plans for adaptive trial designs (Corey 2011) which will be used to rapidly evaluate a variety of prime-boost vaccine regimens in the high prevalence setting of South Africa. The US HIV Military Research Program is also planning a new efficacy trial in men who have sex with men (MSM) in Thailand, using the same or a similar regimen to RV144 but with an additional booster immunization at the 12 month time point (the last shot in RV144 was at six months). This trial is slated to begin in 2014 (Kim 2011).

There is only one ongoing HIV vaccine efficacy trial, HVTN 505. It involves a prime-boost regimen comprising a DNA vaccine followed by an adenovirus serotype 5 (Ad5) vector. The target population is circumcised MSM and male-to-female (MTF) transgender persons who have sex with men. The design of the trial has gone through myriad iterations, and until recently the primary goal was to look at whether the vaccines reduced viral load in recipients who subsequently acquired HIV. In light of the RV144 results, consideration is now being given to expanding HVTN 505 in size so that the effect of vaccination on risk of HIV acquisition can also be evaluated.

Developing New Vectors, Immunogens and Adjuvants

As the term implies, vectors are delivery vehicles—often weakened forms of viruses—that carry vaccine ingredients into the body. Immunogens are the ingredients derived from HIV that the vaccine aims to induce immune responses against, and adjuvants are substances designed to enhance the magnitude and/or quality of those immune responses. The HIV vaccine pipeline contains a variety of vector/immunogen/adjuvant combinations, most commonly administered in prime-boost regimens. New vectors in human trials in 2011 include measles virus, vesicular stomatitis virus (VSV), and a chimpanzee adenovirus (Lorin 2004; Cooper 2008; Rosario 2010). Also in the mix are vaccines that deliver proteins or protein fragments directly, similar to the AIDSVAX envelope protein vaccine used as a booster shot in the RV144 trial.

A novel HIV vaccine vector that has received widespread media coverage due to promising results in macaques is cytomegalovirus (CMV). The vector is under development by the Vaccine and Gene Therapy Institute (VGTI) in collaboration with the International AIDS Vaccine Initiative (IAVI), but has not yet entered human testing. In a study published in the journal Nature, the use of CMV as an SIV vaccine vector led to an unprecedented degree of immunological control of a highly pathogenic challenge virus, SIVmac251 (Hansen 2011). Although large swathes of the human population are already infected with CMV, pre-existing immunity to the vector is not considered an issue because the virus has evolved immune evasion mechanisms that allow it to re-infect (Hansen 2010). There is, however, an important caveat about the use of CMV that was conspicuously absent from press reports about this study; over the last couple of decades, evidence has accumulated that CMV infection has an array of pernicious long-term effects on human health, contributing to cardiovascular disease (Stassen 2006), earlier mortality (Simanek 2011), and a type of immune system damage called immunosenescence that is associated with morbidity and mortality as people reach old age (Pawelec 2011). Although researchers are attempting to render CMV vectors safe for human use, it is currently unclear if—and how—safety can be sufficiently demonstrated to allow clinical trials.

New approaches to immunogen design attempt to improve the ability of vaccines to induce immune responses against a broad array of HIV targets. Oxford University and Tomas Hanke are testing HIVconsv, an immunogen incorporating fourteen parts of HIV that are highly conserved among multiple different clades (Létourneau 2007). Mosaic HIV immunogens represent another approach with the same goal; human testing is anticipated to start within the next year (Corey 2010).

Adjuvants that have ambled into clinical trials since the last TAG pipeline report include heat shock protein 70 (Hsp70), a naturally occurring protein under study as an enhancer of mucosal immune responses (Lehner 2004), and the cumbersomely-named cytokine

granulocyte-macrophage colony-stimulating factor (GM-CSF for short), which the company GeoVax is investigating as an adjuvant for its DNA/MVA vaccine after obtaining promising results in macaques (Lai 2011).

The multitude of candidates in the HIV vaccine pipeline prompts the question of how products will be selected for advancement into efficacy trials. At one time, the major criteria were the nature and magnitude of the anti-HIV immune responses invoked by the vaccines in early studies, along with evidence from pre-clinical research in the SIV/macaque model. However, one of the implications of the RV144 trial is that current immune response assays and animal models may not necessarily predict protective efficacy in humans (the ALVAC/AIDSVAX combination performed dismally by both criteria). It has also become clear that ostensibly similar regimens can induce immune responses that differ substantially in quality, with unclear implications for their effectiveness (Pillai 2011). The uncertainty regarding predictors of success is an additional motivation behind HVTN's adaptive efficacy trial design proposal, which allows for multiple parallel trials of different vaccine approaches with pre-planned interim analyses for the purpose of both rapidly discarding ineffective candidates and quickly identifying and advancing those showing promise (Corey 2011).

Inducing Neutralizing Antibodies

Scientists continue to wrestle with the spiky problem of inducing antibodies that can effectively inhibit HIV. As described in last year's report, several new broadly neutralizing antibodies have been isolated from HIV positive individuals and their structures and targets are now being characterized in detail (Davenport 2011; Pancera 2010; Pejchal 2010; Zhou 2010). There has also been potentially significant progress in understanding how these rare antibodies are generated by the immune system. The production of antibodies by B cells involves a complex process called somatic hypermutation. Essentially, a B cell that is stimulated to make antibodies undergoes several rounds of division during which the genetic code for producing the antibody is shuffled each time, leading to alterations in the antibody structure. If the B cell's genetic mutations produce an antibody with an improved ability to glom onto its target, the cell is selected to undergo more rounds of division. Repeated cycles of this mutation and selection process (referred to as "affinity maturation") lead to the generation of antibodies with a high affinity for their targets. Typically, affinity maturation takes an average of around 10-15 mutations. Remarkably, the broadly neutralizing antibodies against HIV that have been identified show evidence of a more arduous affinity maturation process involving more than 60 mutations. The next step for vaccine researchers is to figure out whether this complex pathway can be recapitulated with a vaccine, leading to the generation of similarly effective antibodies. Signs so far are encouraging, but considerable work remains (Kwong 2011).

TABLE 2. PrEP and Microbicides Pipeline 2011

Product	Type	Manufacturer/Sponsor	Status
Viread (tenofovir)	Nucleotide reverse transcriptase inhibitor	Gilead Sciences/NIAID/CDC	Phase III
Truvada (tenofovir/ emtrictabine)	Combined nucleoside and nucleotide reverse transcriptase inhibitors	Gilead Sciences/NIAID/CDC/University of Washington	Phase III
Truvada (tenofovir/ emtrictabine)	Combined nucleoside and nucleotide reverse transcriptase inhibitors	Gilead Sciences/HIV Prevention Trials Network	Phase II
TMC278LA	Non-nucleoside reverse transcriptase inhibitor, long-acting injectable formulation	St Stephens Aids Trust	Phase I
Ibalizumab (formerly TNX-355)	Monoclonal antibody	TaiMed Biologics Inc., Aaron Diamond AIDS Research Center, Bill and Melinda Gates Foundation	Phase I
Tenofovir gel	Reverse transcriptase inhibitor	CONRAD/CAPRISA/NIAID	Phase IIb
Dapivirine (TMC120) gel	Reverse transcriptase inhibitor	International Partnership for Microbicides	Phase I/II
Dapivirine (TMC120) vaginal ring	Reverse transcriptase inhibitor	International Partnership for Microbicides	Phase I/II
UC-781	Dapivirine (TMC120) vaginal ring	BioSyn	Phase I

Preexposure Prophylaxis

Preexposure prophylaxis (PrEP) is the prophylactic use of antiretroviral drugs to prevent HIV infection. In late 2010, the long-awaited first human PrEP efficacy results were announced and published in the *New England Journal of Medicine* (Grant 2010). The trial, named iPrEx, recruited 2,470 MSM and 29 transgender women at high risk of HIV infection, assigning them to receive daily Truvada (a combination pill containing the antiretrovirals tenofovir and emtrictabine) or placebo. Trial sites were located in Brazil, Ecuador, Peru, South Africa, Thailand, and the United States. Over an average of 1.2 years of follow up, the risk of acquiring HIV infection was reduced by 43.8% among participants in the Truvada arm compared to the placebo arm, a highly statistically significant result. There were a total of 36 infections in Truvada recipients compared to 64 in those on placebo. Additional follow up from May through August 2010 was reported in February of this year: the number of HIV infection endpoints increased to 48 vs. 83 for a final efficacy estimate of 42% (with a 95% confidence interval of 18-60%) (Grant 2011). Importantly, there was a strong correlation between adherence to the PrEP regimen and protection; a subset analysis of the Truvada arm comparing individuals with detectable drug levels to those without found that the presence of drug was associated with

a greater than 90% reduction in HIV acquisition risk. However, this analysis also revealed that drug levels were undetectable in around half the participants assigned to Truvada, providing an indication that adhering to daily PrEP was problematic for a large proportion of the trial population.

In terms of tolerability, relatively few side effects were reported. Only nausea and unintentional weight loss of 5% or more were reported more frequently in the Truvada arm compared to placebo (in both cases, these side effects were noted by around 2% of Truvada recipients vs. 1% placebo). There were a total of five confirmed cases of elevated creatinine, a potential marker for kidney toxicity, all in the Truvada group. Four out of five of these individuals stopped and then restarted the drug without a recurrence of the problem. No other abnormal laboratory values were reported. No cases of drug resistance were observed in the participants who became HIV infected during the trial. However, there were three instances of resistance to emtrictabine documented among 10 people who were found to have had undetected, pre-seroconversion HIV infection at the time of study enrollment.

The iPrEx research team, led by Robert Grant at UCSF, now has funding from NIAID to conduct an open label evaluation (dubbed iPrEx OLÉ) of Truvada as PrEP; all participants from the original randomized trial are being invited to participate. The goals for the study are to assess whether knowledge regarding Truvada's efficacy has any effect on adherence and/or sex practices, and also to gather more safety data over a longer period of follow up.

The iPrEx data has generated considerable excitement in the PrEP field, but results are pending from trials being conducted in other populations. In a sobering development announced earlier this year, a trial of Truvada as PrEP at sites in Kenya, Malawi, South Africa, and Tanzania (the FEM-PrEP trial, sponsored by Family Health International) was stopped midstream after a review by the Data and Safety Monitoring Board (DSMB) found that it would not be able to show efficacy even if carried to completion. The DSMB decision was based on the observation that 56 HIV infections had occurred, evenly divided between the placebo and Truvada arms. The explanation for the FEM-PrEP outcome is as yet unclear.

The US Centers for Disease Control and Prevention (CDC) is sponsoring two ongoing PrEP efficacy trials: one is evaluating tenofovir (Viread) compared to placebo in 2,400 injection drug users in Thailand, the other is looking at Truvada in a population of 2,000 heterosexual men and women in Botswana. The University of Washington is comparing tenofovir to Truvada as PrEP in a trial involving 3,900 serodiscordant couples in Kenya and Uganda. The Microbicide Trial Network's VOICE study has successfully completed enrolment of 5,000 African women and will compare three strategies: oral PrEP using

tenofovir or Truvada and a tenofovir-containing vaginal microbicide gel. A recent DSMB review of VOICE gave it the green light to continue; follow up is due to end in June 2012 with results becoming available in early 2013.

The evidence from iPrEx regarding the difficulty of adhering to daily PrEP has renewed interest in intermittent dosing strategies. The HIV Prevention Trials Network (HPTN) is launching the "ADAPT" study (Alternate Dosing to Augment PrEP Tablet-taking, also known as HPTN 067) which plans to compare 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 compare tolerance, acceptability and drug levels.

Since the 2010 TAG pipeline report two novel PrEP agents have entered phase I trials:

- TMC278LA is a long-acting, injectable formulation of the approved antiretroviral drug rilpivirine that is being studied at four sites in the UK under the sponsorship of the St Stephens Aids Trust.

- Ibalizumab is a monoclonal antibody delivered via intermittent injection; it interferes with the interaction between HIV and the CD4 molecule, thereby inhibiting infection. Studies in people with HIV have documented significant viral load reductions (Bruno 2010). The phase I trial of ibalizumab as PrEP is unusual in that it is recruiting HIV negative volunteers at risk for HIV infection; normally, early-phase studies are restricted to participants with low or no risk of exposure to the virus.

Microbicides

Microbicides are substances that aim to prevent HIV infection via application to the vagina or rectum prior to (and in some cases also after) sex. Last year witnessed the first major microbicide breakthrough with the announcement of the results of CAPRISA 004, a phase IIb trial of tenofovir gel conducted in South Africa (Abdool Karim 2010). Women randomized to receive the gel had a statistically significant 39% reduction in risk of acquiring HIV infection. In raw numbers, there were 38 infections in the group of 445 tenofovir gel recipients and 60 among the 444 placebo recipients over an average of 18 months of follow up. The product was well tolerated and there was a strong association between drug levels in cervicovaginal fluid and protection from HIV (Kashuba 2010), echoing the findings from iPrEx and adding to the plausibility of the result.

Unexpectedly, CAPRISA 004 also showed that tenofovir gel offers significant protection against HSV-2 infection. Risk of acquiring HSV-2 was reduced by 51% (95% confidence interval: 30-78%) among women assigned to the active gel arm. This impressive finding suggests that tenofovir gel could have a dual impact on susceptibility to HIV, because HSV-2 infection is associated with an approximately 3-fold increase in relative risk of HIV acquisition in women (Freeman 2006). Tenofovir only inhibits HSV-2 at very high concentrations that cannot be achieved with oral dosing, but pharmacologist Angela Kashuba has shown that the gel form can reach sufficient levels in the genital tract (Kashuba 2010).

Since the initial presentation of the CAPRISA 004 results at the International AIDS Conference in Vienna in July 2010, the US Food and Drug Administration (FDA) has indicated that two additional confirmatory trials would provide sufficient data for the agency to consider the product for licensure. One trial, VOICE (described in the previous section), is ongoing. A second, called FACTS 001, has taken longer to secure funding than was anticipated, but is now expected to begin in South Africa in August 2011. The fate of a third tenofovir gel efficacy trial planned by the UK's Microbicide Development Programme, MPD 302, is less certain.

Gilead Sciences has licensed the rights to produce tenofovir gel to the non-profit organization CONRAD, which is exploring options for manufacturing and marketing globally. CONRAD has recently announced that the South African government's Technology Innovation Agency (TIA) will be granted the rights to manufacture and distribute tenofovir gel in Africa. TIA has, in turn, set up a joint venture called ProPreven consisting of TIA, Cipla Medpro and iThemba Pharmaceuticals. ProPreven will handle the registration, manufacturing and marketing of the gel if and when the data accrue to support licensure. A recent modeling study based on the results of CAPRISA 004 concluded that, over a twenty year period, the use of tenofovir gel in South Africa could avert up to two million new HIV infections and a million AIDS deaths (Williams 2011).

The next microbicide product that appears likely to undergo efficacy testing is a gel form of the nonnucleoside reverse transcriptase inhibitor drug dapirivine, which is being developed by the International Partnership for Microbicides (IPM). Phase I/II trials have shown that dapirivine gel can be safely delivered via a matrix intravaginal ring (Nel 2009), and IPM has ambitious plans to conduct two phase III efficacy trials of the approach involving a total of 6,000 women.

TABLE 3. Research Toward a Cure

Clinical Trial	ClinicalTrials.gov Identifier(s)	Manufacturer/Sponsor
SB-728-T, autologous CD4 T-cells genetically modified at the CCR5 gene by zinc finger nucleases	NCT01044654 NCT00842634 NCT01252641	Sangamo Biosciences
Vorinostat (SAHA)	NCT01319383 NCT01365065	Merck/University of North Carolina Chapel Hill/ NIAID/Bayside Health
Disulfiram(Antabuse)	NCT01286259	University of California, San Francisco/ Johns Hopkins University
IL-7, DNA/Ad5 HIV vaccine, ART intensification	NCT01019551 NCT00976404	Cytheris/Vical/GenVec, NIH Vaccine Research Center/Objectif Recherche Vaccins SIDA (ORVACS)
Alpha interferon intensification	NCT01295515	NIAID

Not so long ago, prospects for an HIV cure were deemed so dim that even mentioning the word was generally frowned upon, lest it create false hopes. But it is important to appreciate that this semantic reticence did not equate to an absence of research; most of the trials and approaches included in the table above were in development long before the breakthrough case of Timothy Brown was reported. What Brown's experience has done, however, is provide invaluable momentum for the research effort while at the same time bringing the possibility of a cure into the public consciousness. The elevated profile of the field has also spurred a flurry of review articles and opinion pieces in the scientific literature, delineating the challenges that lie ahead (Deeks 2010; Lafeuillade 2011; Lewin 2011a; Lewin 2011b; Margolis 2011; Siliciano 2010).

While the term "cure research" is now increasingly invoked, it is not well defined. In terms of human trials, current strategies can be divided into three broad categories:

- Cell-protecting: approaches designed to protect potential target cells from HIV infection, e.g. via gene therapy.
- Reservoir-depleting: approaches that aim to reduce the amount of residual HIV that persists after viral replication is suppressed by ART.
- Immune-enhancing: approaches to bolster the immune response to HIV in hopes of enabling the body to control or even gradually eliminate residual viral reservoirs.

Sangamo Biosciences is pursuing a cell-protecting strategy based on a proprietary technology that allows targeting of specific genes. By pairing zinc finger proteins with enzymes called nucleases that can break up DNA, Sangamo's approach disrupts the CCR5 gene and thus prevents expression of the CCR5 co-receptor on modified cells (Urnov 2010). 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 re-infused. Presentation of preliminary phase I results early in 2011 generated considerable excitement because the researchers were able to document significant CD4 T cell count increases and persistence of CCR5-deleted CD4 T cells at low but detectable levels in peripheral blood (Lalezari 2011). In a small subset of participants who underwent sampling from the gastrointestinal tract there was evidence that the majority of CD4 T cells in their gut were CCR5-deleted, suggesting that the modified cells had a particular survival advantage in this location, which is known to be a major site of HIV replication (Tebas 2011). Further results from these trials are eagerly anticipated. Unlike many cash-strapped biotech companies, Sangamo is better positioned to move its candidate HIV therapy through the pipeline due to a robust revenue stream obtained from licensing their gene modification technology for laboratory and agricultural use. Researchers are also collaborating with Sangamo to study the effects of CCR5-deleted stem cells in individuals with HIV who require stem cell transplants for AIDS-related lymphoma; the trial is not yet open for enrollment but is slated to take place at the City of Hope in Los Angeles (Cannon 2011).

While Sangamo ultimately has marketing ambitions for its gene therapy, the other examples of cure-related trials are more exploratory in nature. Laboratory experiments indicate that a class of anticancer drugs called HDAC inhibitors can activate the otherwise silent latent HIV reservoir and one such drug—vorinostat (SAHA)—is now being studied for this purpose in both the US and Australia (the principal investigators are David Margolis at the University of North Carolina and Sharon Lewin at Monash University, respectively). The downside of HDAC inhibitors is a daunting toxicity profile that has led these trials to proceed with extreme caution. The goal is not to develop vorinostat but rather to find out if HDAC inhibition can have measurable effects on the HIV reservoir in humans; a positive outcome would justify investment in the development of safer candidates with similar mechanisms of action. Two large pharmaceutical companies, Merck and Gilead, have publicly acknowledged having research programs looking at HIV latency reversal and Merck is involved in the vorinostat trials for this reason.

Disulfiram (Antabuse) is an approved drug used to treat alcoholism, its HIV latency-reversing properties emerged from a large drug screening study conducted by the laboratory of Robert Siliciano at Johns Hopkins University (Xing 2011). The discovery is a testament to the impact of the recently formed amfAR Research Consortium for HIV Eradication (ARCHE), which funded the work of Siliciano and collaborator Steve Deeks at the University of California San Francisco; Deeks's group is now conducing a small trial to investigate whether disulfiram has an effect on latent HIV reservoirs in vivo.

Objectif Recherche Vaccins SIDA (ORVACS) is a foundation based in France that was originally established to support therapeutic HIV vaccine research. ORVACS is sponsoring two trials, Eramune 01 and 02, that are investigating combination approaches to HIV reservoir reduction. Eramune 01 will look at intensifying standard antiretroviral therapy (ART) with the integrase inhibitor raltegravir and CCR5 inhibitor maraviroc, with or without the addition of the cytokine IL-7. Eramune 02 employs the same ART intensification, with or without the addition of a DNA/Ad5 prime-boost therapeutic vaccine developed by the Vaccine Research Center at the National Institutes of Health.

At the National Cancer Institute, an alternate means of ART intensification is being explored. Frank Malderelli's research group is conducting a pilot study of the cytokine alpha interferon as an adjunct. The trial was motivated by an observation that individuals co-infected with HIV and hepatitis C may have declines in residual HIV viral load levels during alpha interferon treatment.

Although only a limited number of clinical trials can reasonably be described as cure-related at the current time, this is likely to rapidly expand. Plans are afoot at the AIDS Clinical Trials Group (ACTG) to investigate a PD-1 inhibitor made by Merck; this approach is intriguing as it may have the potential to both enhance the immune response to HIV and activate latent viral reservoirs (Kaufmann 2009; DaFonseca 2010). The company VIRxSYS has therapeutic vaccine candidate, VRX1273, that is on the verge of phase I; the construct is unusual in that it consists of a lentiviral vector based on HIV itself (Lemiale 2010). Many older gene therapies and therapeutic vaccines that remain in the pipeline (see Tables 4 and 5) could potentially fit under the new rubric of "cure-related" (and may eventually feature in trials for that purpose), because they aim to protect susceptible cells from HIV or improve immune responses to the virus.

If appropriate circumstances arise, researchers also intend to try and duplicate the case of Timothy Brown. This is a complex goal as it involves identifying people with HIV and cancer requiring stem cell transplantation, then finding a matched donor who lacks the CCR5 receptor (in genetic terms, a donor homozygous for the CCR5Δ32 mutation). The doctors involved in Brown's case, led by clinician Gero Hütter, are spearheading this ongoing effort (Hütter 2011).

On 11 July 2011, the National Institutes of Allergy and Infectious Diseases (NIAID) announced the award of three large grants to support HIV cure research under the aegis of a program called the Martin Delaney Collaboratory (named after the late activist and founder of Project Inform who championed the cause of cure-related research). The recipients comprise teams organized by the University of North Carolina, the Fred Hutchinson Cancer Research Center in Seattle, and the University of California, San Francisco in collaboration with the Vaccine and Gene Therapy Institute of

Florida. The total amount of funding is anticipated to be $70 million over five years. Additional information on the projects is being made available via a new website: http://martindelaneycollaboratory.org/.

Immune-Based & Gene Therapies

The developmental pathway for these types of candidate HIV therapies is particularly complex. Because of the effectiveness of antiretroviral drugs in treating HIV, IBTs and gene therapies needs to be able to supplement their effects, or replace them (either intermittently or permanently); the latter goal obviously overlaps with the idea of a "functional cure" described in the previous section.

There are potential opportunities for supplementing ART because a proportion of HIV-positive individuals experience persistent immune dysfunction despite suppression of viral replication to undetectable levels. The features of this dysfunction typically include poor recovery of CD4 T cell numbers in peripheral blood, persistent skewing of the CD4:CD8 T cell ratio (usually around 2:1 in healthy individuals but often <1 in people with HIV), elevated immune activation and inflammation, decreased numbers of naive CD4 and CD8 T cells and increased numbers of dysfunctional, worn-out CD4 and CD8 T cells that are termed "senescent" (Deeks 2011; Erikstrup 2010; Fernandez 2006; Massanella 2010; Robbins 2009). The senescent cells resemble those that have been shown to accrue in very elderly individuals without HIV infection. The most significant risk factor for experiencing these persistent immunological perturbations on ART is initiating treatment at a low CD4 T cell count. Importantly, research shows that there is a link between these phenomena and an increased risk of illness and mortality (Kesselring 2011; Schechter 2006; Zoufaly 2011); therefore, therapies capable of enhancing the restoration of the immune system might be able to improve the prognosis for this subset of people with HIV. Currently the cytokine IL-7 appears to be the only IBT with any prospect of being evaluated for clinical benefit in this setting. There are however several other approaches that attempt to address different aspects of immune dysfunction, including anti-inflammatories and bone marrow stimulants.

Table 4. Immune-Based & Gene Therapy Pipeline 2011

Product	Type	Manufacturer/Sponsor	Status
Maraviroc (Selzentry)	CCR5 inhibitor	Pfizer	Phase IV
Chloroquine phosphate	Anti-inflammatory, anti-inflammatory	NIAID/ACTG	Phase II
Hydroxychloroquine	Antimalarial, antirheumatic, anti-inflammatory	Medical Research Council/Wellcome Trust/ St Stephens Aids Trust	Phase II Phase I

Pegasys (peginterferon alfa-2a)	Cytokine	NIAID/Hoffmann-La Roche	Phase II
Interleukin-7 (CYT 107)	Cytokine	Cytheris	Phase II
HLA-B*57 cell transfer	Cell infusion	NIH Clinical Center	Phase I
TXA127	Bone marrow stimulant, angiotensin 1-7	Tarix Pharmaceuticals	Phase I
Mesalamine (5-aminosalicylic acid)	Oral anti-inflammatory drug approved for the treatment of inflammatory bowel disease	University of California–San Francisco/Salix Pharmaceuticals	Phase IV
Umbilical Cord Mesenchymal Stem Cells (UC-MSC)	Adult stem cells originating from the mesenchymal and connective tissues	Beijing 302 Hospital	Phase I//II
Ganeden BC30, GBI-30, PTA-6086	Probiotic Dietary Supplement	AIDS Healthcare Foundation/Ganeden Biotech, Inc.	Phase II
Etoricoxib	Cox-2 inhibitor, anti-inflammatory	Oslo University Hospital	Phase II
Simvastatin	HMG-CoA reductase inhibitor, anti-inflammatory	University of Pennsylvania, NIAID	Phase IV
OZ1 ribozyme gene therapy	Antiviral ribozyme targeted against the tat gene, introduced into CD4 T cells via stem cells	Johnson & Johnson	Phase II
Lexgenleucel-T (formerly referred to as VRX496)	Lentiviral vector encoding antiretroviral antisense, introduced into CD4 T cells ex vivo	VIRxSYS	Phase II
HGTV43	Vector encoding antiretroviral antisense, introduced into CD4 T cells ex vivo	Enzo Biochem	Phase II
M87o	Entry inhibitor gene encoded by a lentiviral vector, introduced into CD4 T cells ex vivo	EUFETS AG	Phase I
SB-728	Autologous T-cells genetically modified at the CCR5 gene by zinc finger nucleases	University of Pennsylvania/ Sangamo Biosciences	Phase I
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
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 re-infuses them	University of Pennsylvania	Phase I

Anti-inflammatories

The antimalarial drugs chloroquine phosphate and hydroxychloroquine are being assessed for their potential to reduce immune activation and improve CD4 T cell recovery in individuals on ART. A very small pilot trial of chloroquine phosphate that was published last year reported significant reductions in markers of immune activation over two months of treatment (Murray 2010).

Mesalamine is an oral anti-inflammatory drug that acts particularly on the cells of the gut (Iacucci 2010), and the US Food and Drug Administration has approved it for the treatment of ulcerative colitis, proctitis, and proctosigmoiditis. The research group of Steve Deeks at the University of California–San Francisco (UCSF) is conducting a small study to ascertain if mesalamine can reduce inflammation levels in HIV-positive people on ART. The study is motivated by evidence that leakage of normally friendly gut bacteria into systemic circulation (microbial translocation) contributes to immune activation in HIV infection (Brenchley 2006) and is associated with poor immune reconstitution on ART (Marchetti 2008). The same research group has also probed the contribution of CMV co-infection to immune activation in people on ART by conducting a trial of the anti-CMV drug valganciclovir. The study, now published, found that markers of activation on CD8 T cells were significantly reduced by this intervention, suggesting suppression of CMV replication could have benefits in co-infected people with HIV (Hunt 2011a). Unfortunately the toxicity profile of valganciclovir makes it a poor candidate for chronic use, so safer anti-CMV therapies will be needed in order for this potential lead to be followed.

A number of investigators are evaluating whether the approved CCR5 inhibitor maraviroc can dampen immune activation and enhance immune reconstitution. Results from two trials presented at the Conference on Retroviruses and Opportunistic Infections in 2011 were not particularly encouraging, however. In one uncontrolled, single-arm experiment markers of immune activation were reported decrease (Wilkin 2011), but in the other randomized placebo-controlled study these markers increased in blood and gut samples (Hunt 2011b). In neither case did CD4 T cell counts increase significantly.

Two new clinical trials are looking at the anti-inflammatory effects of the pain medication etoricoxib and the lipid lowering agent simvastatin in HIV, respectively. The etoricoxib trial is enrolling people naive to ART due to a prior study finding that the drug reduced immune activation and improved T cell function in individuals for whom ART was not indicated based on European guidelines (Pettersen 2011). Researchers at the University of Pennsylvania are recruiting individuals off ART for their study of simvastatin, in order to assess if the drug can reduce the monocyte inflammation and inflammatory cytokine production that has been linked to brain disease in HIV.

Cell Infusion and Gene Therapies

In addition to being involved in the Sangamo Biosciences trials described in the section on research toward a cure, Carl June's research group at the University of Pennsylvania is evaluating a different gene therapy that modifies CD8 T cells ex vivo, equipping them with a T cell receptor (TCR) that is particularly adept at recognizing HIV-infected cells (Varela-Rohena 2008). The souped-up CD8 T cells are then expanded and re-infused back into the individual. The ultimate goal is to combine both CD4 and CD8 T cell gene

therapy approaches in order to enhance the ability of both subsets to deal with HIV.

Last year, researcher John Rossi from City of Hope in Los Angeles published results from a phase I trial of a combined gene therapy approach in HIV-infected individuals undergoing hematopoietic stem cell (HSC) transplantation for AIDS-related lymphoma (DiGiusto 2010). Genes encoding three different anti-HIV RNA molecules were introduced into a subset of transplanted HSCs in four individuals, and long-term persistence in multiple cell lineages was demonstrated, albeit at very low levels. Although no therapeutic effect could be demonstrated, the study offers evidence that the concept is feasible. Rossi's group is now collaborating with Paula Cannon at the University of California at Los Angeles (UCLA) and Sangamo Biosciences to study the deletion of the CCR5 gene in HSCs, in the same setting of AIDS-related lymphoma.

IL-7

The cytokine IL-7 plays a key role in supporting T-cell development and the proliferation and survival of naive and memory T-cells. Results from two phase I trials of IL-7 in people with HIV reported substantial increases in CD4 and CD8 T-cell counts even at the lowest dose (Levy 2009; Sereti 2009). The cytokine was well tolerated. A new glycosylated form of IL-7 that allows less frequent administration is currently in phase II trials. The manufacturer is a French company named Cytheris. The ACTG is considering the possibility of studying the clinical effects of IL-7 in individuals with poor CD4 recovery despite HIV suppression.

The ability of IL-7 to reduce HIV reservoirs is also under investigation, but there is debate regarding its potential in this setting; while viral load blips were observed in one phase I study (Sereti 2009), it has been argued that the source of this virus was not long-lived reservoirs (Imamichi 2011). Furthermore, it has been shown that under some circumstances IL-7 may expand the number of latently HIV-infected CD4 T cells by stimulating their division (Chomont 2009).

TABLE 5. Therapeutic Vaccines Pipeline 2011

Product	Type	Manufacturer/Sponsor	Status
DCV-2	Autologous myeloid dendritic cells pulsed ex vivo with high doses of inactivated autologous HIV-1.	University of Barcelona	Phase II
HIV-1 Tat vaccine (ISS T-002)	Tat protein vaccine at two different doses (7.5 micrograms or 30 micrograms) in five or three immunizations	National AIDS Center at the Istituto Superiore di Sanità, Rome	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

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/Impfstoffwerk Dessau-Tornau/University of Oxford/UK Medical Research Council Thymon	Phase I/II Phase I/II
MVA-mBN120B	Multiantigen MVA vector	Bavarian Nordic	Phase I
Autologous dendritic cell HIV vaccine	Autologous dendritic cells pulsed with conserved HIV-derived peptide	University of Pittsburgh	Phase I
Multiepitope DNA	Twenty-one CTL epitopes and proprietary, non-HIV derived "universal" CD4 T-cell epitope	Pharmexa-Epimmune	Phase I
Tat vaccine	Recombinant protein	Sanofi Pasteur	Phase I
DC vaccine	Autologous dendritic cells generated using GM-CSF and interferon alpha, loaded with lipopeptides and activated with lipopolysaccharide	Baylor University/Agence Nationale de Recherche sur le Sida et le hepatitis (ANRS)	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
PENNVAX-B biological: 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
GSK HIV Vaccine 732462	p24-RT-Nef-p17 fusion protein in proprietary adjuvant AS01B	GlaxoSmithKline	Phase II
HIV-v	Lyophilised mixture of polypeptide T-cell epitope sequences	Seek	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
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
MVA.HIVconsv	MVA vector	University of Oxford/Medical Research Council	Phase I
GTU-Multi-HIV B clade vaccine, IL-2, GM-CSF, HGH	Multi-antigen DNA vaccine being studied in combination with IL-2, GM-CSF and human growth hormone (HGH)	Imperial College London/Medical Research Council	Phase I
Vacc-4x	Synthetic peptides from the HIV-1 Gag p24 protein + adjuvant	Bionor Immuno	Phase IIb
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

Opal Immunotherapy	Blood cells pulsed with HIV-1 clade C peptides and reinfused	Medicines Development Limited/Phillip T. and Susan M. Ragon Foundation/Imperial College London	Phase I
MAG-pDNA vaccine, GENEVAX™, TriGrid™	Multi-antigen 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
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

Therapeutic Vaccines

The proposal that therapeutic vaccination might enhance the immune response to HIV was floated soon after the virus was first discovered. But clinical trials of a variety of candidates proved consistently disappointing, with no clear evidence of benefit. The most publicized was a large clinical endpoint study of Jonas Salk's candidate, Remune, which showed no significant differences in health outcomes between vaccine and placebo (Khan 2000). The arrival of combination ART lessened the need for a therapeutic vaccine, but also opened up a window of opportunity because it became possible to try and induce new immune responses to HIV without interference from the potentially immune-suppressive effects of ongoing viral replication. An array of therapeutic vaccines are undergoing testing in this context.

Scientists at the University of Barcelona published the first data on their dendritic cell-based approach earlier this year (Garcia 2011). A small but statistically significant viral load reduction was observed in the vaccine recipients, along with some evidence for an inverse association between HIV-specific T cell responses and viral load. The company Argos Therapeutics is also developing a dendritic cell-based therapeutic vaccine, with the twist that it is "personalized" by loading the cells with viral RNA from the person who is going to receive the vaccine; the goal is to induce immune responses that are exquisitely specific to each individual's HIV infection (Routy 2010).

Italian researcher Barbara Ensoli at the National AIDS Center at the Istituto Superiore di Sanità in Rome continues to plug away with studies of a therapeutic Tat protein vaccine that has been in development for over a decade now. Ensoli and colleagues took the dubious step of publishing interim results from an ongoing trial in people on ART, claiming a variety of beneficial effects associated with vaccination, including reductions in markers of immune activation (Ensoli 2010).

A novel approach to therapeutic immunization that recently entered human testing is Opal Immunotherapy. Developed by Stephen Kent's research group at the University of Melbourne, it involves repurposing sets of overlapping peptides derived from HIV that are normally only used in laboratories to measure T cell responses against the virus. Kent had the idea to try and use the peptides as a vaccine by mixing them with either peripheral blood mononuclear cells (PBMC) or whole blood, then infusing this mixture. Studies in SIV-infected macaques have shown some promise (De Rose 2008) and a phase I trial is now underway.

An alternate strategy being pursued by some therapeutic vaccine manufacturers is immunization of HIV-positive people prior to any significant CD4 T-cell decline, with the aim of delaying the need for ART. At the 2010 International AIDS Conference, results from a 60-person randomized controlled study of this type were reported, showing that a DNA vaccine manufactured by FIT Biotech lowered viral load by around half a log after two years of follow up. A small but statistically significant increase in CD4 T cell counts was also observed (Vardas 2010).

The largest pharmaceutical company involved in this research area is GlaxoSmithKline. Their vaccine candidate, obscurely designated 732462, consists of a fusion protein including several HIV antigens (p24, p17, reverse transcriptase and Nef) in a proprietary adjuvant, AS01B. GSK is conducting a phase II trial exploring the potential for immunization to delay the need for ART.

Conclusion

As incremental as it may be, there is no doubt that significant progress has occurred over the past few years. Until quite recently, there was no evidence of efficacy from any vaccine, microbicide, or PrEP trial. But the investment in research is starting to pay off, and while it may be frustrating that no product is yet available, there is definitely light at the end of these pipelines.

For cure research, the shift from the laboratory to clinical trials is only just beginning. But there is already hope in the form of Timothy Brown, and an increasing demand for science to push beyond the ART-for-life paradigm that currently prevails. The rising profile of cure research is also providing a welcome opportunity for immune-based and gene therapies to emerge from relative obscurity and enter the mainstream.

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The Hepatitis C Treatment Pipeline

BY TRACY SWAN

Special thanks to Juliana Chan and Polly Clayden

Dedicated to Luis Mendão: brilliant activist and delightful human being.

The Thrill Is Already Gone

In May of 2011, a long-awaited improvement in the standard of care for hepatitis C virus (HCV) became reality: the US Food and Drug Administration (FDA) approved the first direct-acting antivirals (DAAs), Merck's boceprevir (Victrelis) and Vertex's telaprevir (Incivek). But excitement about these new drugs has already been overshadowed by a triple-whammy: the first proof-of-concept that hepatitis C can be cured without peginterferon (PEG-IFN) and ribavirin (RBV); reports of better drugs on the horizon; and challenges in clinical care, including the complexity and cost of new HCV regimens, a critical shortage of specialists to administer HCV treatment, and lack of infrastructure for treatment delivery.

Evolution to Revolutionary?

In April 2011, groundbreaking results from a 21-person pilot study were announced: after only 24 weeks of treatment with two oral DAAs, a protease inhibitor and an NS5a inhibitor from Bristol-Myers Squibb, four of ten people were cured. Quad therapy (with peginterferon and ribavirin added) was even more effective, curing nine of ten people.[1]

For now, the success of HCV treatment rests largely upon response to peginterferon. Hopefully, peginterferon will become a therapeutic relic as the standard of care for HCV continues to evolve. The next batch of DAAs may cure more people in less time than triple therapy with peginterferon, ribavirin, and boceprevir or telaprevir. Trials are exploring DAA combinations without peginterferon; some are using it only when DAAs do not fully suppress HCV. Although ribavirin plays an essential role at present, there may be equally effective and more tolerable replacements in the future.

Clinical Issues in the United States

> "The availability of DAA therapy will forever change the landscape of HCV, in that we will be able to cure patients of disease who we were unable to cure in the past. Unfortunately, this medical breakthrough will be coupled with resource scarcity… The influx of patients requesting HCV therapy will present a significant problem…On average, a health care provider can reasonably initiate therapy on only three patients each week before exceeding their work capacity… we anticipate at least 500 requests for evaluation for HCV therapy within the first few weeks of DAA availability, [so] current staffing will be unable to meet the demands of all patients with HCV."
>
> –Andrew Aronsohn and Donald Jensen,"Distributive Justice and the Arrival of Direct-Acting Antivirals: Who Should Be First in Line?"

The current challenge—to fully realize the benefits of boceprevir and telaprevir by avoiding drug resistance and treatment failure—is immediately ahead of us. In the United States, there are not enough specialists to meet current demand for HCV treatment. Many have "warehoused" patients in anticipation of better treatment, and are not seeing any new patients. At the same time, patient management is becoming more complex, involving response-guided therapy and drug-specific treatment algorithms. We are not prepared for the anticipated surge in HCV treatment uptake triggered by more effective treatment.

Access Issues

> "…And, please, let me talk about money. In Spain, we received the news about the price of boceprevir and telaprevir in the US with incredulity. We are indignant, and we do not understand how pharmaceutical companies can justify these outrageous prices. Western society has given the private sector the opportunity to research and develop treatment, but this doesn't entitle you to charge disproportionate prices. At a time when cuts are causing the closure of entire hospital units, emergency rooms and a variety of medical services in this country, how do you expect us to be able to advocate for your new drugs?"
>
> Xavi Franquet, European Community Advisory Board and Grupo de Trabajo sobre Tratamientos del VIH, Sitges IV Meeting, June 2011

Most of the 130 to 170 million people who are living with chronic hepatitis C will not be cured, because HCV treatment is too expensive. Many high-burden countries cannot afford to offer hepatitis C testing, let alone treatment. Although efforts to produce generic peginterferon are underway, access to HCV treatment remains limited or nonexistent.

In the United States, 48 weeks of peginterferon and ribavirin costs more than $30,000. Boceprevir-and telaprevir-based regimens halved treatment duration for 44% (boceprevir) to 58% (telaprevir) of study participants [2,3,4]. But any possible savings on peginterferon and ribavirin are offset by the cost of HCV protease inhibitors (see Table 1. Cost of HCV Treatment with a Protease Inhibitor in the United States).

Diagnostics

Unfortunately, the boom in drug development has not been accompanied by innovative and affordable diagnostics for HCV, and point-of-care viral load testing for monitoring response to treatment. There is no single test for acute-stage HCV, and diagnosis of chronic hepatitis C remains an expensive two-step process. In many parts of the world, people do not have access to HCV testing. Even when HCV RNA testing is accessible, the process can be overly cumbersome, since people have to return for a second testing visit without being given a diagnosis. Research to streamline HCV diagnostics with a single inexpensive test should proceed in tandem with drug development.

TABLE 1. Cost of HCV treatment with a protease inhibitor in the United States

(Does not include: HCV RNA testing and other labs, medical visits, and additional medications for side effects)

Drug, duration, price range	Early response	Slow response	Responder/relapser	Partial and null responders*	People with cirrhosis
Boceprevir Total duration: 28-48 weeks $45,227 to $80,675 (with PegIntron)	24 weeks of boceprevir $26,400 (+PEG/RBV for 28 weeks at $18,827)	32 weeks of boceprevir $35,200 (+PEG/RBV for 48 weeks at $32,275)	32 weeks of boceprevir $35,200 (+ PEG/RBV for 36-48 weeks at $24,206–$32,275)	32 weeks of boceprevir $35,200 (+ PEG/RBV for 36-48 weeks at $24,206–$32,275)	44 weeks of boceprevir $48,400 (+PEG/RBV for 48 weeks at $32,275)
Telaprevir Total duration: 24-48 weeks $65,322 to $81,445 (with Pegasys)	12 weeks of telaprevir $49,200 (+ PEG/RBV for 24 weeks at $16,122)	12 weeks of telaprevir $49,200 (+ PEG/RBV for 48 weeks at $32,245)	12 weeks of telaprevir $49,200 (+ PEG/RBV for 24-48 weeks at $16,122–$32,245)	12 weeks of telaprevir $49,200 (+PEG/RBV for 48 weeks at $32,245)	12 weeks of telaprevir $49,200 (+PEG/RBV for 48 weeks at $32,245)

*Boceprevir labeling suggests that people with <0.5 $\log_{10}$ drop in HCV RNA at week 4 are likely to be null responders; they were not included in the phase III trial for treatment-experienced people.

Public and private payers are sure to balk at the cost of DAAs, and are likely to impose restrictive treatment eligibility criteria and other barriers, such as prior authorization and

top-tier pricing, making access difficult. It is unfortunate that payers are the strongest recourse for price controls.

Research Issues

HCV clinical trials are going to become even more complex, with the advent of triple therapy (peginterferon and ribavirin plus boceprevir or telaprevir). Different dosing schedules will make it difficult to assess efficacy of a single drug and to compare regimens. Boceprevir and telaprevir need to be taken every eight hours, while most second-generation DAAs are once-a-day drugs. Blinded trials will require twice-daily placebo with once-daily drugs. People who are taking a once-daily drug plus placebo may skip their only dose of active drug, placing them at higher risk for treatment failure and drug resistance, since adherence is known to worsen with more frequent dosing requirements. The advantages of a once-daily drug may be obscured by placebo.

HCV clinical trials must incorporate drug- and patient-specific considerations. Treatment algorithms and stopping rules differ for each drug and according to the population it is studied in. Host and viral factors, such as IL28B genotype, stage of liver disease, race/ethnicity, age, HCV subtype (1a versus 1b), and prior response to HCV treatment must also be taken into account. Designing clinical trials and interpreting their results will become more and more of a challenge.

Cure rates with telaprevir- and boceprevir-based regimens are high, making it more difficult for other DAAs to demonstrate superiority. Non-inferiority trials will be needed for the next generation of drugs. These agents are likely to offer other advantages, such as shortened treatment duration, simpler regimens, and more convenient and tolerable drugs. Hopefully regulators and sponsors will consider non-traditional endpoints, such as treatment duration and discontinuations for adverse events, and type, incidence and severity of side effects, along with efficacy. Tolerability and convenience are also extremely important to people who will be taking these drugs.

Plea For Simplicity

Interpreting data from complex clinical trials and translating them directly into clinical practice is difficult, particularly in the absence of a standing, multidisciplinary treatment guidelines panel, an approach that has optimized HIV treatment outcomes and facilitated reimbursement by public and private payers. Simplicity should become a major focus of HCV drug development.

Most Need, Least Data

Merck and Vertex chose not to conduct early access trials in people with urgent need, who were ineligible for their clinical trials. Early access trials could have saved lives, and allowed physicians to gather information about if and how HCV protease inhibitors could be used in patients who need them most. It is likely that boceprevir and telaprevir will be used in desperate patients, regardless of the lack of information about their safety and efficacy. It is time for the pharmaceutical industry to work with regulators, physicians, and activists to launch early access trials.

Unfortunately, boceprevir and telaprevir are not going to be able to get the job done for people with poor prognostic factors, urgent need, and peginterferon intolerance. Prior null responders with cirrhosis did not reap much benefit; adding telaprevir to peginterferon and ribavirin increased the cure rate from 10% to only 14%, and there are limited data on boceprevir in this population.[5]

Safety and efficacy of boceprevir and telaprevir are not yet known in HIV/HCV coinfected people (although pilot studies are ongoing, and larger ones planned). No studies have been initiated in children, the elderly, people with renal insufficiency, or liver transplant candidates and recipients (although there have been no pharmacokinetic studies of boceprevir and telaprevir is not recommended for people with hepatic impairment).

Despite low enrollment of African Americans in registration trials for boceprevir and telaprevir, it is clear that adding one of these drugs significantly increased rates of sustained virological response (SVR; meaning no hepatitis C can be detected six months after treatment completion; regarded as a cure) over PEG-IFN/RBV (see Table 2. Translating Trial Results into Clinical Practice: Boceprevir and Telaprevir in Treatment-Naive Persons). But there are lingering questions about the optimal duration of boceprevir-based therapy in African Americans, since the SVR among African Americans was 11% lower for response-guided therapy versus 48 weeks of treatment.[3]

Unfortunately, data on SVR among Latinos/Latinas are scarce. Latinos and Latinas comprised less than 10% of treatment-naïve study participants in telaprevir phase III trials Nonetheless, telaprevir did boost SVR among treatment naïve Latinos/Latinas; SVR rates ranged from to 70% to 94%, a significant improvement over peginterferon and ribavirin.[2,4] Merck did not provide any data on boceprevir in Latinos and Latinas.

Drug-Drug Interactions

HCV protease inhibitors share metabolic pathways with medications that are commonly used by people with hepatitis C. Drug-drug interactions can lead to drug resistance and HCV treatment failure when levels of an HCV protease inhibitor are too low, or worsen side effects when they are too high. In turn, HCV protease inhibitors may decrease levels of other drugs to sub-therapeutic levels, or increase them to toxic levels.

Interactions between antiretroviral agents and DAAs complicate HIV treatment; a single drug or entire regimen may need to be switched before initiating hepatitis C treatment. This is tricky, because HIV/HCV coinfected people have limited options for treating their HIV while on HCV treatment; in the ongoing telaprevir coinfection trial, participants could either use an efavirenz-based regimen (with a higher dose of telaprevir) or a boosted atazanavir-based regimen (other HIV protease inhibitors cannot be used with telaprevir, due to significant drug-drug interactions).[6] Unfortunately, data on boceprevir drug-drug interactions are limited to efavirenz (which lowers boceprevir levels) and tenofovir.[7]

Since hepatitis C is highly prevalent among current and former injection drug users, drug-drug interaction studies with DAAs and opioid substitution therapy (OST) must be a priority. If DAAs are used in people on OST without this information, a range of consequences may occur, including HCV drug resistance and treatment failure, drug overdose, or withdrawal symptoms. So far, it has been established that telaprevir reduces methadone levels; although dose adjustment may not be needed, clinical monitoring is recommended. A drug-drug interaction study of telaprevir and buprenorphine is underway. Unfortunately, there are no drug-drug interaction data on methadone and buprenorphine for boceprevir, save the warning in the label, which reads "Plasma concentrations of methadone or buprenorphine may increase or decrease when coadministered with VICTRELIS [boceprevir's brand name]. However, the combination has not been studied. Clinical monitoring is recommended as the dose of methadone or burenorphine may need to be altered during concomitant treatment with VICTRELIS."

Current Research Landscape

Are You Experienced?

The FDA has categorized treatment-experienced people into three groups:

Responder-Relapser: HCV RNA undetectable at end of treatment with peginterferon and ribavirin, but HCV RNA detectable within 24 weeks of treatment follow-up.

Partial Responder: greater than or equal to 2 $\log_{10}$ (99%) reduction in HCV RNA at week 12, but not achieving HCV RNA undetectable at end of treatment with peg-interferon and ribavirin.

Null Responder: less than 2 $\log_{10}$ (99%) reduction in HCV RNA at week 12 of treatment with peginterferon and ribavirin.

People who could not tolerate treatment or do not know their prior response are not included; nor are people who experienced viral breakthrough during treatment.

There are dozens of HCV clinical trials underway, but most are for treatment-naïve participants. Of the nine phase II/III HCV protease inhibitor trials, six are open to treatment-experienced participants (some may be limited to responder-relapsers and partial responders). Current phase II polymerase and NS5a inhibitor trials offer few options: treatment-experienced participants are eligible for only one of three NS5a inhibitor trials, one of two nucleoside/nucleotide polymerase inhibitor trials, and one of seven non-nucleoside polymerase inhibitor trials.

At present, an estimated 750,000 people in the United States (and thousands more in Western Europe) have been unsuccessfully treated for hepatitis C. Treatment-experienced patients are likely to be first in line for treatment with new HCV drugs; financial experts project that by 2013 they will comprise at least two-thirds of the market share for DAAs. The population of treatment-experienced people is large, and will continue to grow once the first generation of hepatitis C protease inhibitors have been widely used. More trials exploring DAA combinations and treatment strategies are needed for treatment-experienced people.

Multi-DAA/quad therapy trials will help to clarify the best approach based on HCV subtype, treatment history and other factors. Abbott, Boehringer Ingelheim, Bristol Myers Squibb (BMS), Genentech, Gilead, Merck, Pharmasset, and Vertex have opened in-house combination trials.

A single company may not have all of the most exciting drugs, so cross-company clinical collaborations are needed to optimize HCV treatment. BMS and Pharmasset, who have very exciting DAA candidates, launched the first cross company clinical collaboration; in May of 2011, they announced a peginterferon-sparing trial combining BMS's NS5a

inhibitors with one of Pharmasset's nucleotide polymerase inhibitors (PSI-7977), with or without ribavirin.

In July 2011, Pharmasset announced another clinical collaboration with Tibotec/Medivir, pairing PSI-7977 (its nucleotide analog) with TMC435 (a protease inhibitor), with and without ribavirin in a phase II trial of prior null responders with HCV genotype 1. The trial will be launched in the third or fourth quarter of 2011. These joint ventures are crucial for identifying best-in-class regimens and optimizing HCV treatment.

Boceprevir and Telaprevir

Improvements in HCV treatment (such as response-guided therapy and drug- and patient specific treatment algorithms) bring a new level of complexity to clinical care, making it unappealing to inexperienced providers. During FDA approval hearings for boceprevir and telaprevir, an antiviral advisory committee member remarked that the amount of knowledge required to treat HCV approaches the complexity–if not the wisdom–of a Talmudic scholar. Complexity brings consequences, such as greater potential for errors in prescribing and administering treatment, higher dropout rates from poorly managed side effects, and increased risk for drug resistance and treatment failure.

Clinicians and their patients will have a choice between boceprevir and telaprevir-based treatment. Although they are in the same class, these drugs are used differently. Boceprevir requires a four-week "lead-in" with peginterferon and ribavirin to lower on-treatment failure and relapse rates; telaprevir is initiated along with peginterferon and ribavirin. With each drug, there may be a peginterferon and ribavirin "tail" after triple therapy, lasting 12 to 36 weeks.

Telaprevir offers treatment-naïve patients a less complex treatment algorithm, higher cure rates, and a better chance to shorten treatment than boceprevir, but tolerability may be an issue. More than half of the participants in all phase III trials were afflicted with rash (versus 32% for PEG/RBV alone). Although most cases were mild-to-moderate, 1% suffered severe rash, and a subset of these cases (<1%) experienced Stevens Johnson Syndrome (SJS, a rare, life-threatening reaction to a medication or infection) or Drug-Related Eruption with Systemic Symptoms (DRESS, another severe drug reaction).

Boceprevir worsens the hemotologic side effects of peginterferon and ribavirin, especially anemia. During phase III trials, more than 40% of participants in the boceprevir arms were treated with epoetin alfa, a red blood growth cell factor.[3,8] Red blood cell growth factors carry a warning about increased mortality, serious cardiovascular and thromboembolic events, stroke and risk of tumor progression or recurrence in cancer patients. They are also expensive, adding at least $500 per week to the cost of HCV treatment. Anemia can also be managed by reducing the dose of ribavirin, but this strategy may reduce treatment efficacy; an ongoing trial of boceprevir-based treatment is comparing ribavirin dose reduction to epoetin alfa use.

TABLE 2. Translating trial results into clinical practice: Boceprevir and telaprevir in treatment-naive persons

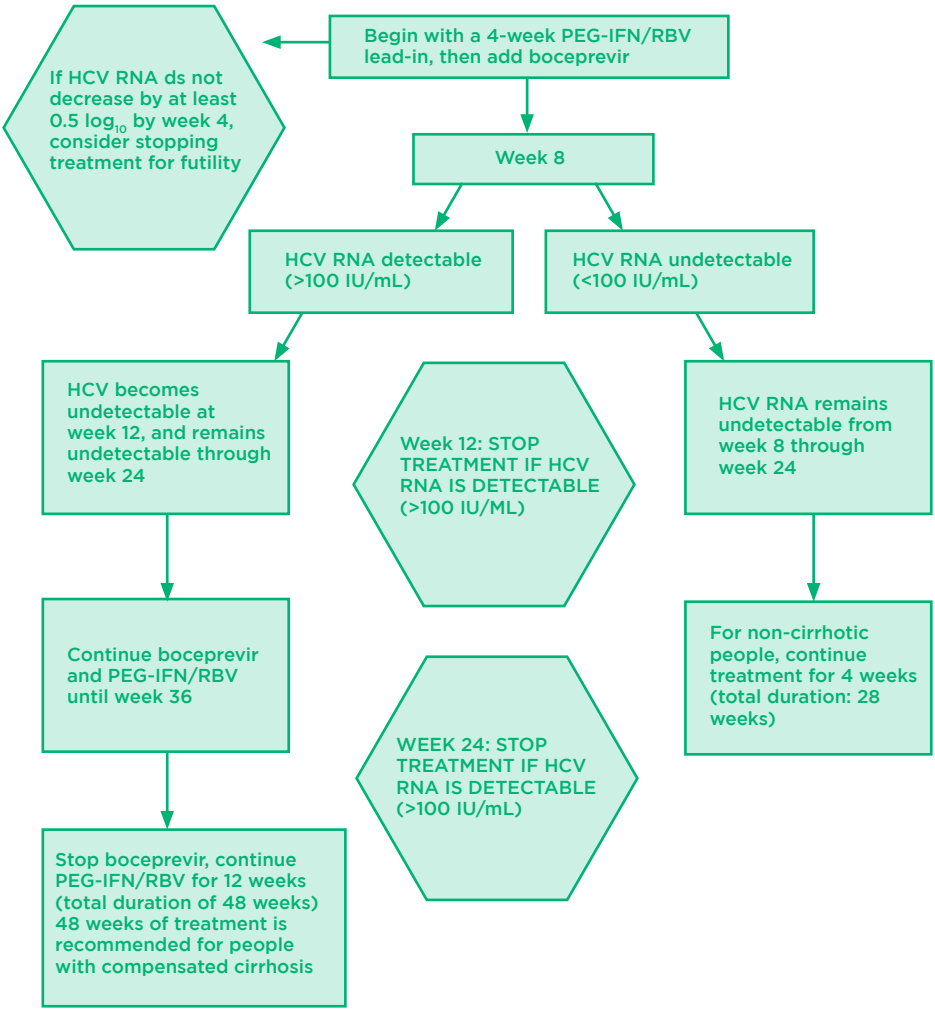
Characteristic	Boceprevir	Telaprevir
Lead-in	Yes; 4 weeks of PEG/RBV	No
Dosing	750 mg, every 7–9 hours, with food (meal or light snack); 12 pills/day	800 mg, every 7–9 hours with food (not-low fat); 6 pills/day.
Treatment duration	28–48 weeks	24–48 weeks
Eligible for 24-28 weeks of treatment	44%	58–60%
Adverse events	Anemia, neutropenia, thrombocytopenia, dysgeusia, dry mouth, vomiting and diarrhea	Mild to severe rash, itching, anemia, ano-rectal itching and burning, hemorrhoids, elevated bilirubin and uric acid, gout, thrombocytopenia and gastrointestinal events
Discontinuation for adverse events	14%	10–19%
SVR, overall	63–66%	72–79%
Relapse rate	9%	9%
SVR, African Americans	42–53% (~14% of participants)	65% (range: 50-94%) (~10% of participants)
SVR, Latinos/Latinas	Data not provided	79% (range: 70-94%) (~10% of participants)
SVR, bridging fibrosis or cirrhosis	41-52% (~11% of participants)	53–88% (~8% of study participants)
SVR, people on methadone maintenance	No data	33% (only 11 patients in phase III trials)
SVR, HIV/HCV coinfected people	Ongoing pilot studies; data are not yet available. Drug-drug interactions with HIV protease inhibitors and non-nucleosides; coadministration not recommended (except efavirenz)	Ongoing pilot study; data are not yet available. Cannot be used with boosted darunavir, fosamprenavir, and lopinavir; tenofovir levels are increased; monitoring recommended.
Use in hepatic and renal impairment	No dose adjustment required for mild, moderate and severe hepatic impairment; no data in decompensated cirrhosis; no dose adjustment required for renal impairment	Should not be used in people with moderate to serious hepatic impairment, since drug exposure is reduced; exposure increased in renal impairment; analysis of single-dose study underway to see if dose adjustment or multiple dose study is required
Drug-drug interactions	An extensive list is available in the prescribing information, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202258lbl.pdf (accessed May 14, 2011)	An extensive list is available in the prescribing information, available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf (accessed May 25, 2011)
Early access trials	None	None

Sources: FDA briefing documents for boceprevir and telaprevir: available at ttp://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252341.pdf and http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM252561.pdf (accessed May 26, 2011)

Jacobson IM, McHutchison JG, Dusheiko G, et al; ADVANCE Study Team. Telaprevir in combination with peginterferon alfa-2a and ribavirin in genotype 1 HCV treatment naïve patients: final results of phase III ADVANCE study. [abstract LB-2] 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. October 29–November 2, 2010.
Poordad F, McCone J Jr, Bacon BR, et al; SPRINT-2 Investigators. Boceprevir for untreated chronic HCV genotype 1 infection. N Engl J Med. 2011 Mar 31;364(13):1195-206.

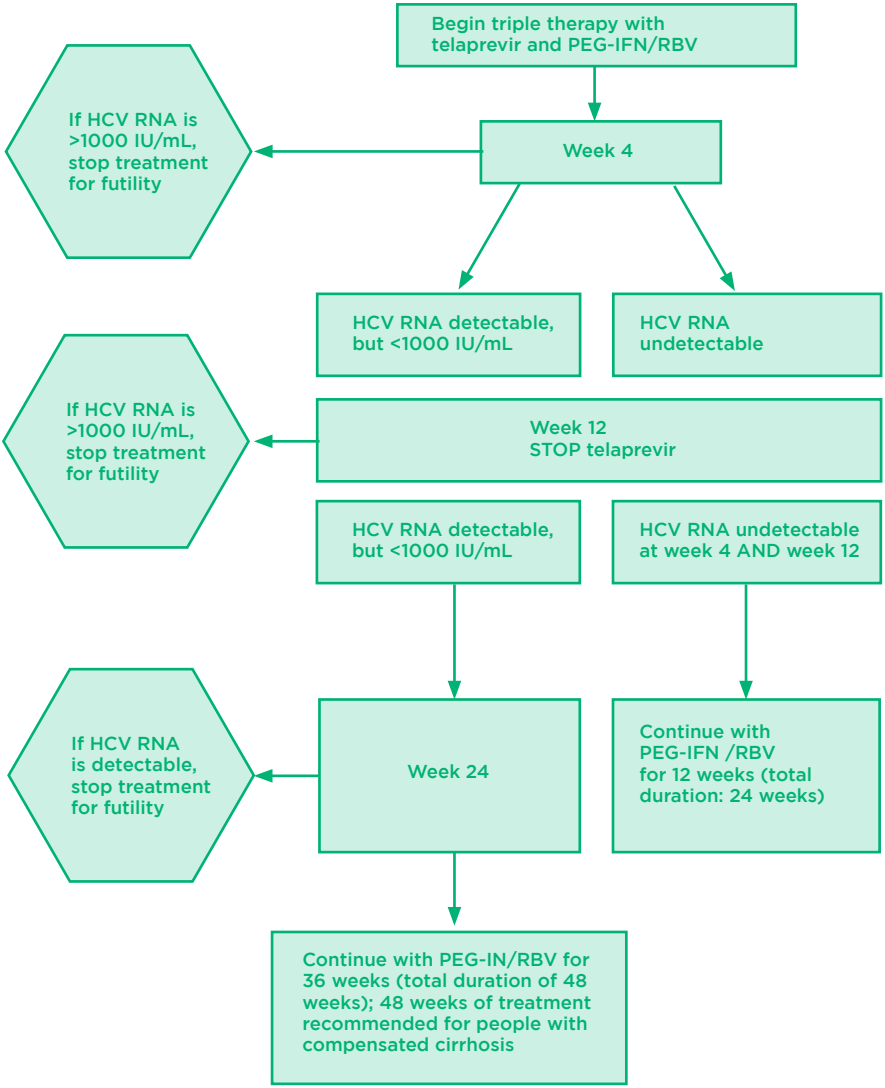
Sherman KE, Flamm SL, Afdhal NH, et al; ILLUMINATE Study Team. Telaprevir in combination with peginterferon alfa-2a and ribavirin for 24 or 48 weeks in treatment-naive genotype 1 HCV patients who achieved an extended rapid viral response; final results of phase III ILLUMINATE study. (Abstract LB-1) 61st Annual Meeting of the American Association for the Study of Liver Diseases. Boston, Massachusetts. October 29 – November 2, 2010.

Fig 1. Boceprevir: Treatment Naïve Algorithm



Source: Prescribing information for boceprevir. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202258lbl.pdf (accessed May 25, 2011).

Fig 2. Telaprevir: Treatment-Naive Algorithm



Source: Prescribing information for telaprevir. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf (accessed May 25, 2011)

TABLE 3. Translating trial results into clinical practice: Boceprevir and telaprevir in treatment-experienced persons

Parameter	Boceprevir	Telaprevir
SVR, responder-relapsers	70–75%	83–88%
SVR, partial responders	40–52%	54–59%
SVR, null responders	Not studied	29–33%
SVR, cirrhosis	F3 and F4 combined: responder-relapsers: 50–83% partial responders: 30–46% null responders: not studied	F3: responder-relapsers: 85% partial responders: 56% null responders: 39% F4: responder-relapsers: 84% partial responders: 34% null responders: 14%
Treatment duration recommended in labeling	For responder-relapsers and partial-responders: 36–48 weeks For people with compensated cirrhosis and prior null responders, 48 weeks of treatment are recommended	For responder-relapsers; 24–48 weeks For people with compensated cirrhosis and partial/null responders: 48 week
Discontinuation for treatment failure	20%	~37%
Discontinuation for AEs	10%	5–13% during telaprevir dosing

Sources: Prescribing information for boceprevir and telaprevir. Available at:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202258lbl.pdf and http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf (accessed May 25, 2011).

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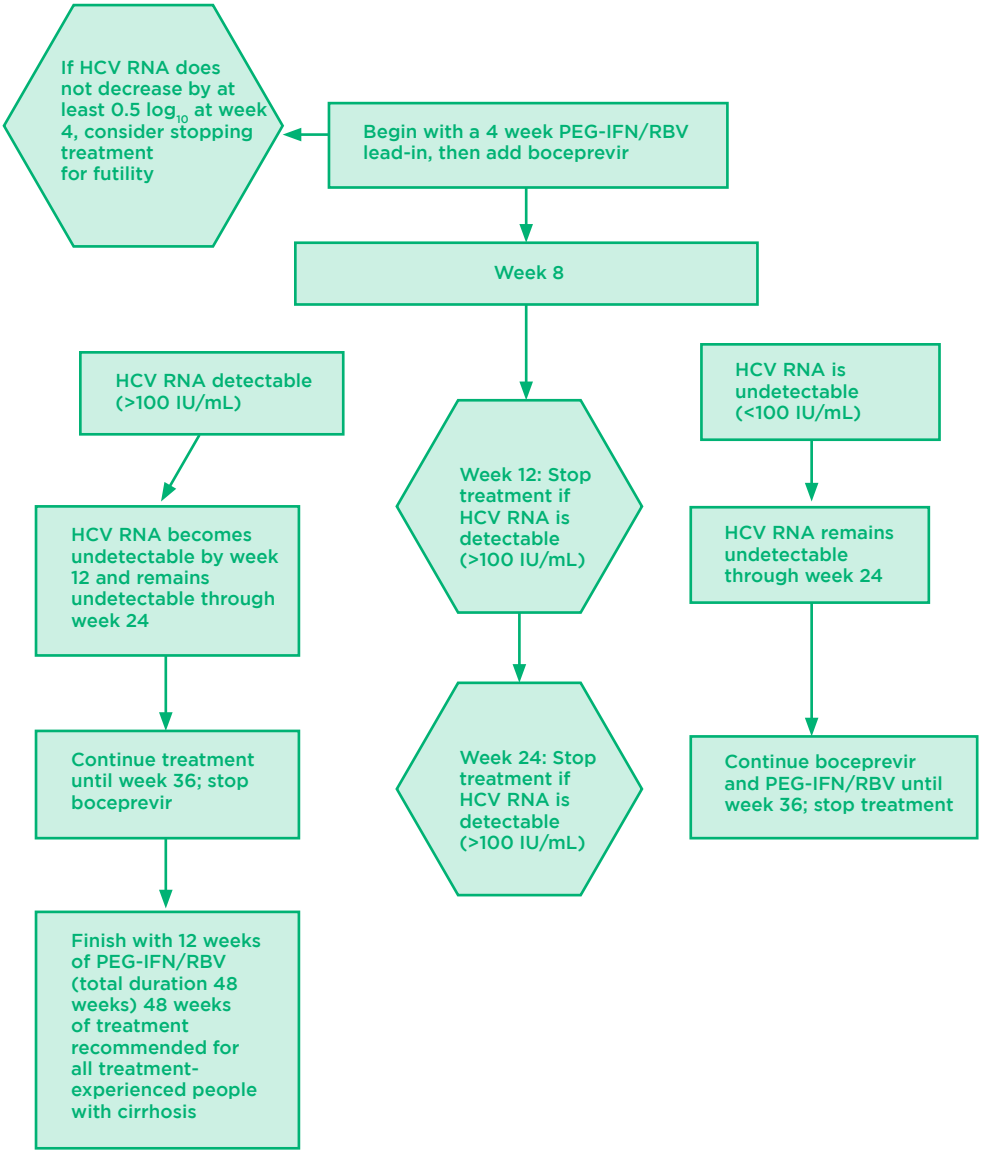
Zeuzem S, Andreone P, Pol S, et al. REALIZE trial final results: telaprevir-based regimen for genotype 1 hepatitis C virus infection in patients with prior null response, partial response, or relapse to peginterferon/ribavirin (Opening and General Session 1) 46th Meeting of the European Association for the Study of the Liver. Berlin, Germany. March 30-April 3, 2011.

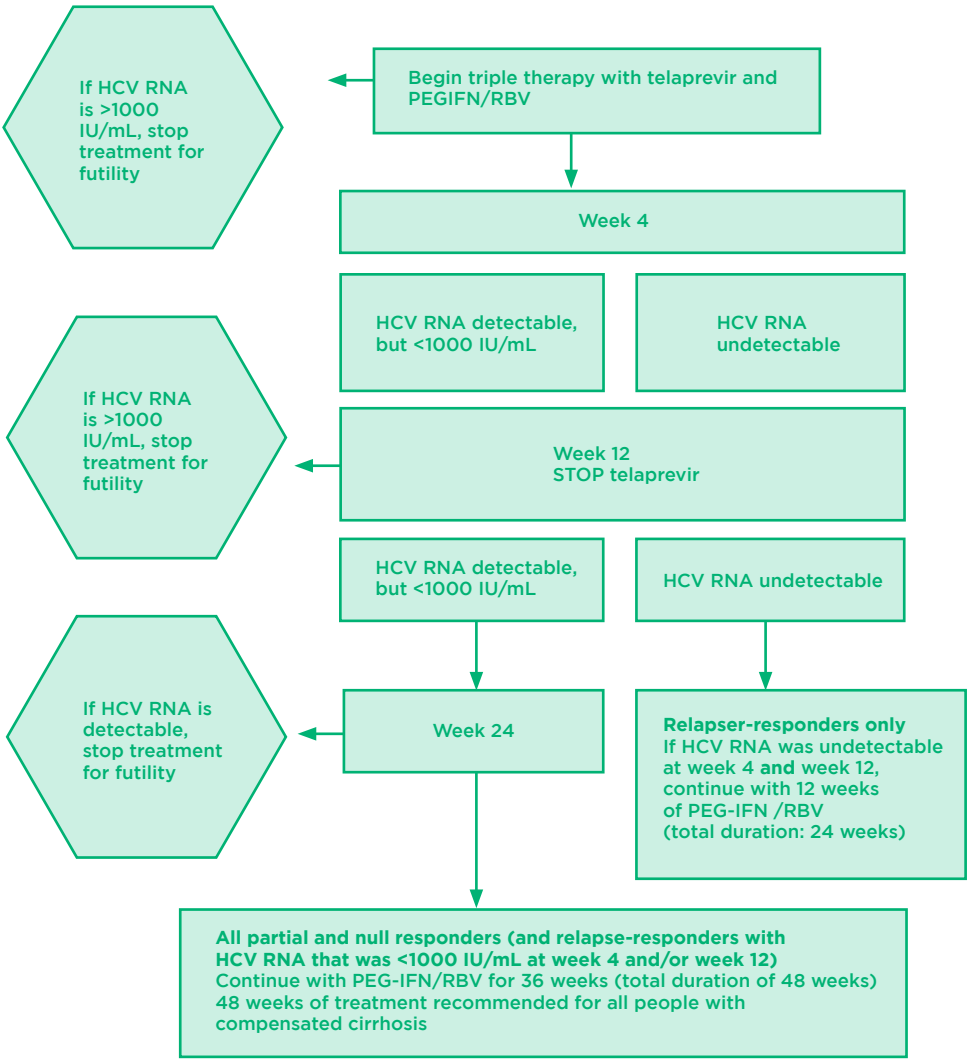
Fig 3. Boceprevir: Treatment-Experienced Algorithm

Data from prior responder-relapsers and partial responders; null responders excluded



Source: Prescribing information for boceprevir. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202258lbl.pdf (accessed May 25, 2011).

Fig 4. Telaprevir: Treatment Experienced Algorithm*



*Telaprevir labeling notes that a high proportion of null responders, especially those with cirrhosis, did not achieve SVR and developed drug resistance.

Source: Prescribing information for telaprevir. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf (accessed May 25, 2011)

HCV Protease Inhibitors

Boceprevir and telaprevir have the market to themselves for the next couple of years, but the next generation of HCV protease inhibitors is already nipping at their heels. These drugs offer advantages such as more convenient dosing, activity against other genotypes, and/or against protease resistant virus. Many are being studied in combination with other DAAs, with and without peginterferon, and with or without ribavirin.

Side effects include anemia, neutropenia, thrombocytopenia, photosensitivity, itching, rash, hemorrhoids, dysgeusia, headache, elevated alanine amino transferase (ALT) and bilirubin, jaundice, elevated uric acid and gout, dizziness, nausea, vomiting, and diarrhea.

TABLE 4. HCV protease inhibitors in development

Agent/Sponsor	Phase and Population	Comments
ABT 450/r Abbott Laboratories	Phase II, HCV genotype 1, treatment-naive (PEG-IFN-free studies limited to people with the IL-28B CC genotype)	Once daily; ritonavir boosted; with PEG-IFN/RBV, and combination with ABT-333 (non-nucleoside polymerase inhibitor) plus ribavirin (not open as of May 2011) With ABT-072 (non-nucleoside polymerase inhibitor) plus ribavirin
ACH-2684	Phase I; healthy volunteers followed by HCV genotypes 1 and 3, treatment-naive	Once daily; pan-genotypic activity
ACH-0141625 Achillion Pharmaceuticals	Phase II, HCV genotype 1, treatment-naive	Once daily dosing; studied with PEG-IFN/RBV
BI 201335 Boehringer Ingelheim	Phase III, HCV genotype 1, treatment-naive, and treatment-naive/treatment-experienced (combination study)	Once daily; with PEG-IFN/RBV for 12-48 weeks (treatment-naive) With PEG-IFN/RBV for 24-48 weeks (treatment-experienced; not open as of 12 August 2011) With BI 207127 (non-nucleoside polymerase inhibitor) with or without ribavirin (treatment-naive)
BMS 650032	Phase II, HCV genotype 1 and 4, treatment-naive; genotype 1, treatment experienced	Twice daily; with BMS 914143 (peginterferon lambda) with ribavirin; with or without BMS 790052 (NS5a inhibitor) 16-48 weeks (treatment-naive) With PEG-IFN/RBV for 24-48 weeks (treatment-naive, genotypes 1 and 4) With BMS 790052 (NS5a inhibitor), with or without ribavirin, and quad (PEG-IFN/RBV) prior null responders: HCV genotype 1b only in dual DAA arm
CTS-127 Conatus	Phase II; HCV genotype 1, null responders	Twice daily; with PEG-IFN/RBV

Danoprevir (formerly ITMN-181 /RG 7227) Genentech/Roche	Phase I/II, HCV genotype 1, treatment-naive and treatment-experienced	Twice daily; ritonavir boosted; with RG7128 (nucleotide polymerase inhibitor), with or without ribavrin (treatment-naive) With PEG-IFNRBV in naive and experienced With ribavrin, with or without RG7128 (nucleotide polymerase inhibitor), with or without PEG-IFN (partial and null responders)
GS9256 Gilead Sciences	Phase II; HCV genotype 1, treatment-naive	Twice daily; with tegobuvir (non-nucleoside polymerase inhibitor), with or without PEG-IFN/RBV
GS 9451 Gilead Sciences	Phase II; HCV genotype 1, treatment-naive	Once daily; with PEG-IFN/RBV, with and without tegobuvir (non-nucleoside polymerase inhibitor) With GS 5885 (NS5a inhibitor), tegobuvir (non-nucleoside polymerase inhibitor), and ribavirin With PEG-IFN/RBV, with and without GS 5585 (NS5a inhibitor), IL 28B CC genotype only; 6-24 weeks of treatment. Not open as of 24 August 2011
GSK 2485852 Glaxo Smith Kline	Phase I; HCV genotype 1, treatment-naive	With and without ritonavir boosting
MK-6335 Merck	Phase I, HCV genotypes 1 and 3, treatment-naive and treatment-experienced	Not open as of May 2011
MK-5172 Merck	Phase I, HCV genotypes 1 and 3; phase II, genotype 1, treatment-naive	Once daily; may be active against resistant virus and across genotypes Phase II study will be the first HCV treatment trial with an HCV protease inhibitor (boceprevir) in the control arm
Vaniprevir (MK-7009) Merck	Phase II in HCV genotype 1, ongoing in treatment-experienced	Twice daily; study completed in treatment-naive; SVR rates were numerically higher than PEG-IFN/RBV + placebo, but the difference was not significant; additional trial in treatment-naive withdrawn

NS5a Inhibitors

Although NS5a inhibitors are very potent, these drugs have a low resistance barrier, especially in HCV genotype 1a. Nonetheless, HCV has already been cured with an NS5a inhibitor combined with a protease inhibitor. This drug class is expected to become an important part of DAA regimens, since NS5a inhibitors may have pan-genotypic activity. So far, little is known about the side effect profile of NS5a inhibitors, since they have mainly been studied with peginterferon, ribavirin, and other DAAs; headache was reported in early studies.

TABLE 5. NS5a inhibitors in development

Agent/Sponsor	Phase and Population	Comments
ABT-267 Abbott Laboratories	Phase II, HCV genotype 1, treatment-naive	Once daily dosing; not open as of May 2011
ACH 2928 Achillion Pharmaceuticals	Phase I expected in mid-2011	Pan-genotypic activity
BMS 790052 Bristol Myers Squibb	Phase II/III HCV genotype 1, treatment-naive and treatment-experienced; HCV genotypes 2 and 3, treatment-naive; In African Americans and Latinos/Latinas with HCV genotype 1, treatment-naïve	With BMS 914143 (peginterferon lambda) and ribavirin, with or without BMS 650032 (protease inhibitor) 16-48 weeks With PSI-7977, with or without ribavirin (genotypes 1, 2, and 3, treatment-naive) With PEG-IFN/RBV (African Americans, Latinos/Latinas, and partial and null responders)
BMS 82483 Bristol Myers Squibb	Phase II	Study withdrawn prior to enrollment
GS 5585 Gilead Sciences	Phase II; HCV genotype 1, treatment-naive	Once daily; with GS 9451 (HCV protease inhibitor), tegobuvir (non-nucleoside polymerase inihibtor) and ribavirin With PEG-IFN/RBV, with or without GS 9451 (protease inhibitor); IL 28B CC genotype only; 6-24 weeks of treatment. Not open as of 12 August 2011
PPI-461 Presidio	Phase Ib, HCV genotype 1, treatment-naive	Once daily dosing (completed)

Non-Nucleoside Polymerase Inhibitors

The hepatitis C virus offers more than one binding site for non-nucleoside polymerase inhibitors, so it may be possible to combine drugs from this class with one another, and with DAAs from other classes. Unfortunately, non-nucleoside polymerase inhibitors are active only against HCV genotype 1, and have a low resistance barrier. Side effects include headache, abdominal pain, nausea, fatigue, rash, and elevated bilirubin.

TABLE 6. Non-nucleoside polymerase inhibitors in development

Agent and sponsor	Phase and population	Comments
ABT 072 Abbott Laboratories	Phase II; HCV genotype 1, treatment-naive; PEG-IFN free studies limited to people with IL28B CC genotype only	Once daily; with PEG-IFN/RBV and with ABT-450/r (protease inhibitor) plus ribavirin
ABT 033 Abbott Laboratories	Phase II; HCV genotype 1, treatment-naive; PEG-IFN free studies limited to people with IL28B CC genotype only	Twice daily; with PEG-IFN/RBV and in combination with ABT-450/r (protease inhibitor), plus ribavirin
Setrobuvir ANA 598 Anadys Pharmaceuticals	Phase II; HCV genotype 1, treatment-naive and treatment-experienced	Twice daily; 28-48 weeks; with PEG-IFN/RBV
BI 207127 Boehringer Ingelheim	Phase I; HCV genotype 1, treatment-naive	Twice or thrice-daily dosing; with BI 201335 (protease inhibitor), with or without ribavirin
BMS 791323 Bristol Myers Squibb	Phase II: HCV genotype 1, treatment naive	Twice daily; with PEG-IFN/RBV
Filibuvir (PF-868554) Pfizer	Phase II, HCV genotype 1, treatment-naive	Twice daily; with PEG-IFN/RBV, 24-48 weeks
Tegobuvir (GS 9190) Gilead Sciences	Phase II, HCV genotype 1, treatment-naive	Twice-daily; with PEG-IFN/RBV With PEG-IFN/RBV and GS 9451 (HCV protease inhibitor) With GS 9451 (HCV protease inhibitor), GS 5885 (NS5a inhibitor), and ribavirin
TMC 647055 Tibotec Pharmaceuticals	Phase I, healthy volunteers and HCV genotype 1, treatment-naive	
TMC 649128 Medivir AB/ Tibotec Pharmaceuticals	Phase Ia; healthy volunteers	
VCH 222 Vertex Pharmaceuticals	Phase I/II HCV genotype 1, treatment-naive	With PEG-IFN/RBV With telaprevir (HCV protease inhibitor) and PEG/RBV (dual therapy arm discontinued)

Nucleoside and Nucleotide Polymerase Inhibitors

Although several candidates never made it out of phase II due to toxicity, the current nucleoside and nucleotide polymerase inhibitor candidates hold great promise. Early results from trials of Pharmasset's PSI-7797 have generated hope that nucleotides may become the next backbone of HCV treatment—or the treatment itself.

Simplicity is king; nucleoside and nucleotide polymerase inhibitors may bypass current complexities of HCV treatment, such as IL28-B genotype, baseline viral load, race, HIV status, and HCV genotype. These drugs are not magic bullets, but nucleosides and nucleotides offer the potential to dramatically simplify and shorten HCV treatment, along with other desirable elements: a high resistance barrier, once-daily dosing, good tolerability, and pan-genotypic activity. Side effects include dizziness, fatigue, headache, and fever.

TABLE 7. Nucleoside and nucleotide polymerase inhibitors in development

Agent/Sponsor	Phase and population	Comments
Nucleotide Polymerase Inhibitors		
GS 6620 Gilead Sciences	Phase I, HCV genotypes 1, 2, and 3; treatment naive	
IDX 184 Idenix	Phase I/II; male healthy volunteers	Originally studied with IDX 320, a protease inhibitor that has been discontinued due to liver toxicity; remains on partial clinical hold. Food effect being studied; phase IIb trial in combination with PEG-IFN/RBV open
INX-189 Inhibitex	Phase I in HCV genotype 1, treatment-naive has been completed	Once-daily dosing; FDA has fast-tracked development; Phase II expected in Q2/Q3 of 2011
PSI-938	Phase I, HCV genotype 1, treatment-naive	Once daily, studied in combination with PSI 7797; Phase II combination trials, with and without ribavirin, are expected in mid-2011
PSI 7797	Phase I/II; HCV genotype 1, treatment-naive; followed by HCV genotypes 4,5,6; also being studied in HCV genotypes 2 and 3, treatment-naive	Once-daily; with PEG-IFN/RBV for 12-24 weeks With PEG-IFN/RBV for 12 weeks in HCV genotypes 2 and 3, with ribavirin, with or without peginterferon, and as montherapy for 12 weeks; with PEG-IFN/RBV for 8-12 weeks With PSI 938 for up to 14 days; longer trial expected in mid-2011 With BMS 790052 (NS5a inhibitor), with or without ribavirin

Nucleoside Polymerase Inhibitors		
Mericitabine (RG7128) Genetech/Pharmasset	Phase II, HCV genotype 1 (naive and experienced) and genotype 4, (treatment-naive)	With PEG-IFN/RBV (naive) With ritonavir-boosted danoprevir (protease inhibitor), with or without ribavrin (naive) With ritonavir-boosted danoprevir and ribavirin, with or without PEG-IFN (experienced)
RO5428029 Hoffman-La Roche	Phase I; healthy volunteers	
TMC 649128 Medivir AB/Tibotec Pharmaceuticals	Phase Ia; healthy volunteers	

Host-Targeting Agents

Resistance to host-targeting agents (HTAs) is less likely to occur than DAA resistance, making these drugs an attractive addition to HCV treatment. There are different types of HTAs. Entry inhibitors work by blocking viral entry into host cells. Cyclophilin inhibitors work by binding to cellular proteins that regulate the immune system; some drugs in this class are immunosuppressants. Both Debio 025 and SCY-635 bind to host cell proteins that may facilitate HCV replication without immunosuppressive activity. Cyclophilin inhibitors may have pan-genotypic activity. Unfortunately, resistance to these drugs has been characterized. Side effects include muscle weakness, low platelets, headache, nausea and elevated bilirubin, which was reversible upon discontinuation.

TABLE 8. Host targeting agents in development

Agent/Sponsor	Phase and population	Comments
Alispovir (DEBIO 025) Novartis	Phase II/III; HCV genotype 1, treatment-naive Also genotypes 3 and 3	Loading dose twice daily for 7 days, followed by once daily dosing
ITX 5061 iTherx	Phase Ib; HCV genotype 1, treatment- naive and liver transplant recipients	Once daily
SCY-635 Scynexis Incorporated	Phase II; HCV genotype 1, treatment-naive, IL28B C/T or TT only	Twice daily

Novel Interferons

If DAA combination therapy doesn't pan out for everyone, new types and formulations of interferon will come in handy. These may be more convenient, or more tolerable. For example, peg lambda interferon was more effective at 12 weeks than peginterferon alfa 2a, as well as more tolerable. Flulike symptoms, anemia, neutropenia and thrombocytopenia were significantly lower among people who got peg lambda than peginterferon alfa, although the incidence of depression was similar. Transient elevations in direct bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were reported in the highest-dose peg lambda arm, but resolved when the dose was lowered or discontinued.[9]

Generic peginterferon could make HCV treatment accessible to millions of people who need it. There is at least one generic peginterferon (y-shaped peginterferon alfa 2a) in development, which hopefully will make HCV treatment accessible to the millions who need it and are unable to afford Merck's Peg Intron or Roche's Pegasys. In any case, patents in the United States and Europe will be expiring in 2016 (PegIntron) and 2017 (Pegasys).

TABLE 9. Novel interferons in development

Agent and sponsor	Phase and population	Comments
BMS 914143 (Peg Lambda interferon) Bristol Myers Squibb	Phase II; HCV genotypes 1, 2, 3, and 4, treatment-naive	Once weekly subcutaneous, fixed-dose injection; with ribavirin With ribavirin and BMS 790052 (NS5a inhibitor) and/or BMS 650032 (protease inhibitor) for 16-48 weeks
Locteron Interferon alfa 2b, Controlled Release Formula (CR2B) OctoPlus; Biolex Therapeutics	Phase IIb in HCV genotype 1, treatment-naive has been completed; Phase III has not been announced as of May 2011	Biweekly subcutaneous injection; with ribavirin Lower incidence of depression and flulike symptoms reported in lower-dose Locteron arms, but more severe adverse events than peginterferon alfa 2b
Y-shaped peg interferon alfa 2a Biogeneric Pharma and Xiamen Amoytop Biotech Co	Phase I/III, no HCV genotype specified, treatment-naive	Generic product; subcutaneous, fixed-dose injection, once weekly versus once every ten days, versus biweekly, with ribavirin

Immunomodulators

Exploration of additional ways to stimulate the immune response against HCV continues, with a variety of different approaches, including monoclonal antibodies, therapeutic vaccines, and TLR-7 agonists.

TABLE 10. Immunomodulators in development

Agent/Sponsor	Phase and population	Comments
CHRON-vac C ChronTech Pharma AB and Inovio	Phase II, HCV genotype 1, treatment- naive	Therapeutic vaccine; unique delivery system. Administered once per month, for two months, followed by peginterferon and ribavirin
GI5005 Globe Immune	Phase II, HCV genotype 1, treatment- naive and partial responders (null responders excluded)	Therapeutic vaccine, administered subcutaneously; multiple dosing schedule. Studied as both lead-in to peginterferon and ribavirin and as salvage therapy Expanded to include 40 people with the IL28B TT genotype
GS9260 Gilead Sciences	Phase I; healthy volunteers	TLR-7 agonist; oral drug

For HIV/HCV coinfected people

HCV treatment trials for HIV/HCV-coinfected people are underway, after years of pressure from activists, clinicians, and regulatory agencies. The first two trials, of boceprevir and telaprevir, were slow to enroll because coinfected people did not want to wind up receiving pegylated interferon and ribavirin with placebo (in the control arm). Regulatory guidance has changed since the first boceprevir and telaprevir trials. Regulators have now stipulated that a control arm is not necessary, as SVR with standard of care has been well-documented, and is suboptimal. A single-arm, 300-person study is sufficient for gaining an indication in coinfection.

Unfortunately, drug-drug interactions have limited the options for antiretroviral therapy coadministration with HCV protease inhibitors to date. Hopefully, dual and multiple DAA studies, with and without ribavirin and with and without peginterferon, will be launched as soon as there are data from HCV monoinfection trials and drug-drug interaction studies to support them.

TABLE 11. Trials in HIV/HCV-Coinfected People

Agent/Sponsor	Phase, Population, and Study Size	Comments
BI 201335 (HCV protease inhibitor) Boehringer Ingelheim	Phase III; HIV-1 /HCV genotype 1, treatment-naive and relapsers N=316	With PEG-IFN/RBV comparing 12 weeks of triple therapy followed by 36 weeks of PEG-IFN/RBV versus 24 weeks of triple therapy followed by 24 weeks of PEG-IFN/RBV First large, phase III study of a direct-acting antiviral to include coinfected treatment-naive and treatment-experienced persons Not open as of 24 August 2011
Boceprevir (HCV protease inhibitor) Merck Treatment-experienced trial co-sponsored by French National Agency for Research on AIDS and Viral Hepatitis Rennes University Hospital Schering Plough	Phase II; HIV-1/HCV genotype 1, treatment-naive N=99 Phase II; HIV-1/HCV genotype 1, treatment-experienced N=80	With PEG-IFN/RBV; placebo-controlled study; fully enrolled (opened in 2009) With PEG-IFN/RBV; opened in April 2011 (France only)
Nitazoxanide (antimicrobial) Romark Laboratories (sponsored by National Institutes of Health)	Phase I/II; HIV-1/HCV genotype 1, treatment-experienced N=75	With PEG-IFN/RBV; opened in 2010
Telaprevir (HCV protease inhibitor) Vertex/Tibotec (Treatment-experienced trial co-sponsored by French National Agency for Research on AIDS and Viral Hepatitis)	Phase II; HIV-1/HCV genotype 1, treatment-naive N=68 Phase II: HIV-1/HCV genotype 1, treatment-experienced (null responders with cirrhosis excluded) N=80	With PEG-IFN/RBV; placebo-controlled study; fully enrolled (opened in 2009) With PEG-IFN/RBV; opened in April 2011 (France only)

And More....

Other approaches to HCV treatment are being studied: Santaris Pharma's injectable microRNA inhibitor, SPC3649 is entering phase II; it is being studied in treatment-naive people with HCV genotype 1.

Silymarin, the active ingredient in milk thistle, is being studied in acute viral hepatitis, as monotherapy and with peginterferon and ribavirin in treatment-experienced people.

Conclusion: Getting Ducks in a Row

Investments in research and drug development have paid off for hepatitis C. We need a parallel investment in health care, to fully realize the benefits of therapeutic advances. HCV drug development is moving forward rapidly, but the capacity and resources to treat people with HCV have stalled. Millions of people are without access to HCV treatment; high drug prices and the global fiscal crisis make attainment of universal access a challenge. Access to drugs is not all that is required. HCV care and treatment must be offered with linkage to mental health care, case management services, peer support, addiction treatment, and harm reduction services.

Unfortunately, boceprevir and telaprevir were approved in the absence of treatment guidelines (aside from their prescribing information). Clinicians need information about how best to use these new drugs. Otherwise, therapeutic chaos may ensue, leading to treatment failure and drug resistance.

Our biggest challenge is not curing hepatitis C, it is getting health care systems ready for the people who will be using them, as we prepare people to deal with these fragmented systems. Hepatitis C is prevalent among poor, marginalized people. Many of them struggle with addiction, psychiatric disorders and medical comorbidities as well as socioeconomic challenges such as homelessness, unemployment, poverty and incarceration. Multidisciplinary HCV care and treatment, including peer support and education programs, is effective, and these delivery systems need to be expanded. Developing and marketing new drugs will not cure people; good health care will.

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Additional Resources

www.clinicaltrials.gov
www.hepatitisCadvocate.org
www.hivandhepatitis.com
www.natap.org

The Tuberculosis Diagnostic Pipeline

BY JAVID SYED

Introduction

After a spurt of activity in new tuberculosis (TB) diagnostics and algorithms approved for widespread use by the World Health Organization (WHO), this year the TB diagnostics cupboard is bare, with no new test or strategy expected to be reviewed for WHO approval until next year.

This lull is due to the dearth of investment in new TB diagnostics, despite the still pressing need for a true TB point-of-care (POC) test.

However the TB and TB/HIV program implementers of the world should be busy this year with the important rollout and scale-up of the Xpert MTB/RIF TB test in high-burden countries where the new test—which can diagnose TB and multidrug-resistant tuberculosis (MDR-TB) within two hours rather than the two months of traditional culture—must rapidly be implemented if its lifesaving promise is to be realized.

This 2011 TB diagnostics pipeline focuses on products or strategies likely to be submitted for review by the WHO for use worldwide in the next three years.

From 2007 to 2010, the WHO's Strategic and Technical Advisory Group for Tuberculosis (STAG-TB) reviewed and recommended the widespread implementation of eight new diagnostic tests and strategies (see Table 1).

TABLE 1. Diagnostic Tests Approved by the WHO, 2006–2010*

Recommended Approach	Name of Test	Sponsor/ Developer	Technique	Sample	Measures	Health Systems in Which Test Is Most Likely to Be Used	Year of WHO Approval
Algorithms to improve the diagnosis of smear-negative pulmonary and extrapulmonary TB among adults in HIV-prevalent and resource-constrained settings			Algorithms combining smear test, chest X-rays, culture, HIV test, symptom screen, examination of aspirates from extrapulmonary site of infection, and clinician's judgment to treat	Sputum as well as samples from extrapulmonary sites of infection	TB bacilli, abnormal radiographs, or specific characteristics of extrapulmonary fluid with high protein content	Peripheral or reference laboratories (depending on the test)	2006
Liquid culture	MGIT	BD Diagnostic Systems	Automated liquid culture	Sputum and other specimens from sites of infection	TB growth and drug-resistant TB	Reference laboratories	2007
Rapid speciation test	Capilia test	Tauns, Standard Diagnostics, and FIND	Lateral flow technology that uses antibodies to detect Mycobacterium tuberculosis (MTB)	Culture isolates	MTB DNA	Reference laboratories	2007
Revised case definition of a sputum-positive pulmonary TB case to at least one TB bacilli in one sputum sample		Special Programme for Research and Training in Tropical Diseases (TDR)	Strategy to increase sensitivity of sputum smear microscopy	Sputum	TB bacilli	Peripheral laboratories	2007
Line probe assays for MDR-TB	INNO-Lipa	Innogenetics	Line probe assay that requires culture	Amplified DNA	Rifampicin-resistant mutation in MTB DNA	Reference laboratories	2008
	GenoType MTBDRplus	HAIN Lifescience	Line probe assay that can be done on sputum	Sputum specimen, dried sputum, culture isolates	Isoniazid- and rifampicin-resistant mutation in MTB DNA	Reference or peripheral laboratories	2008

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Front-loaded sputum smear microscopy		TDR	Strategy to prevent dropouts in the diagnostic process by reducing number of clinic visits needed for sputum smear microscopy	Sputum	TB bacilli	Peripheral laboratories	2009
Light-emitting diode (LED) microscopy	LED adaptor for existing microscopes	LW Scientific and Fraen	Fluorescent microscopy	Sputum and other specimens from sites of infection	TB bacilli	Peripheral laboratories	2009
	Primo Star iLED microscopy	Carl Zeiss Inc. and FIND	Fluorescent microscopy	Sputum and other specimens from sites of infection	TB bacilli	Peripheral laboratories	2009
Noncommercial culture and drug susceptibility test (DST)	Microscopic observation drug susceptibility	Academic laboratories	Inverted light microscopy that detects TB growth	Sputum and other specimens from sites of infection	TB growth and drug-resistant TB	Reference laboratories	2009
	Nitrate reductase assay	Academic laboratories	Solid culture; TB growth causes color change	Sputum and other specimens from sites of infection	TB growth and drug-resistant TB	Reference laboratories	2009
	Colorimetric DST	Academic laboratories	Solid culture; TB growth causes color change	Sputum and other specimens from sites of infection	TB growth and drug-resistant TB	Reference laboratories	2009
Cartridge-based automated nucleic acid amplification test (NAAT)	Xpert MTB/RIF	Cepheid, FIND, and University of Medicine and Dentistry New Jersey	Automated NAAT	Sputum	MTB DNA and DNA mutations to identify rifampicin resistance	Peripheral laboratories	2010

**Sources: World Health Organization 2006, 2007a, 2008a, 2009, and 2010a.*

These new tools have the potential to vastly speed up diagnosis and permit prompt initiation of proper treatment for TB. They could bring previously inaccessible technologies closer to patients, improve the accuracy of testing available at peripheral district health centers, and increase the speed with which TB and drug-resistant disease can be confirmed at both peripheral and reference laboratories.

However, none of the newer TB tests is ideal because of the cost, complexity, requirements for electricity, laboratory infrastructure, biosafety equipment, and the need for highly trained staff. The rollout of these newly recommended technologies will be slow and riddled with challenges. No TB test yet recommended by WHO is a true POC test appropriate for health posts—where 60% of people with TB seek services—or household testing (O'Brien 2009).

The lack of scientific investment is the key barrier in TB diagnostics discovery and development. To restore the TB diagnostics pipeline to health, robust, sensitive, and specific biomarkers for MTB infection, disease, and cure need to be discovered and technology platforms developed that can detect them.

Factors Essential in a New TB Diagnostic

The utility of a test is defined by the following factors linked to test accuracy and the place within the health system that 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 a 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 (Stall 2011).

Diagnostic algorithm: An algorithm is a recommended sequence in which tests and procedures—such as symptom screens—can be used for diagnosis and treatment. Even a less-than-perfect test can improve access to treatment depending on how it can be paired with other diagnostic tools in an algorithm.

Where within the health system the test can be used: A test's usefulness depends in part on how decentralized its use can be. In this report the health system is divided into the health posts, peripheral laboratories, and reference laboratories.

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

2. Peripheral laboratories or health centers: These settings 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.

3. Reference laboratories: These sophisticated laboratories serve 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 amplication tests (NAATs) (O'Brien 2009).

TABLE 2. TB diagnostic tests and processes in the pipeline, 2011

Name of Test	Sponsor/Developer	Technique	What It Measures	Estimated Date of WHO Review
Peripheral Laboratories				
Manual loop-mediated isothermal amplification process (LAMP)	Eiken Chemical/Foundation for Innovative New Diagnostics (FIND)	Manual nucleic acid amplification	MTB DNA	2012
Clearview© TB ELISA	Alere	ELISA to detect Lipoarabinomannan (LAM) in urine	MTB LAM antigen	2013
Colorimetric Thin Layer Agar (TLA) DST	London School of Hygiene and Tropical Medicine/FIND	Colorimetric DST by culturing TB on a TLA plate and using microscopy to identify MTB growth	MTB culture growth	2012
Reference Laboratories				
GenoType® MTBDRs/	Hain Lifescience/FIND	Line probe assay to identify drug susceptibility to second-line TB drugs on TB culture isolate; is being tested on sputum samples	MTB DNA indicating resistance to fluoroquinolones, ethambutol, and aminoglycosides/ cyclic peptides (amikcin, kanamycin, capreomycin)	2012
Sensititre® MTB Minimum Inhibitory Concentration (MIC) Plate	TREK Diagnostic Systems	Detects MTB growth in TB antibiotic containing plates to identify drug resistance	TB bacilli	2013

What Is in the TB Diagnostic Pipeline?

At the Heath Post Level

An instrument- and electricity-free POC or lateral flow dipstick test with simple training and no biosafety requirements would be ideal for the health post level. A quick, accurate, noninvasive POC test that allows for same-day results could have a massive impact on early case detection and appropriate treatment initiation. Immediate initiation of treatment would reduce onward transmission of TB (Abu-Raddad 2009; Médecins Sans Frontières/Treatment Action Group/Partners in Health 2009).

Several research avenues are being pursued to reach this elusive POC dipstick test. Volatile organic compounds from the breaths of people with active TB disease are being analyzed using modern technology like gas chromatograph/mass spectroscopy or through less high-tech methods such as using the giant African pouch rat to essentially smell breath and detect TB (Phillips 2010; Poling 2010; Weetjens 2009).

The Foundation for Innovative New Diagnostics (FIND) has identified TB proteins making up 0.5% of the total TB genome that are reactive to serum from persons with active disease. Lead candidate proteins that could be useful for a POC test are being purified (Kunnath-Velayudhan 2010).

Alere is developing Determine™ TB LAM Ag, a lateral flow test for use in health post settings. Similar to Alere's Clearview© TB LAM ELISA test, the Determine test detects lipoarabinomannan (LAM) in urine. LAM is a TB cell wall protein released by metabolically active TB bacteria. The noninvasive test detects TB in unprocessed urine samples, making sample collection easier than sputum collection. Like the Clearview, the Determine assay may be more sensitive in people with HIV with advanced immunodeficiency, a population in which TB is currently hard to diagnose. Alere states that the test can provide results in 25 minutes. Studies are evaluating the usefulness of this test for diagnosing extrapulmonary TB and TB in HIV-positive children (Baker 2011).

No POC test is likely to be ready for STAG-TB consideration in the next three years.

In Peripheral Laboratories

1. The LAMP TB Assay

A loop-mediated isothermal amplification process (LAMP)-based NAAT by Eiken Chemical and FIND is being studied for use in peripheral laboratories. If validated, this manual NAAT could replace microscopy. This closed-system LAMP test does not require heating and cooling, highly trained laboratory workers, or advanced biosafety equipment, as the sputum processing and instrumentation required have been greatly simplified. The prototype is being studied in Japan and elsewhere. The previous version of the test had high sensitivity (97.7%) in smear-positive sputum specimens, but only 48.8% in smear-negative sputum, while the specificity was high at 99% in both (Boehme 2007). No data are available on the sensitivity and specificity of the new prototype. The LAMP test may go before STAG-TB in 2012.

2. The LAM TB ELISA Test

Alere's Clearview TB ELISA test detects LAM protein in urine within three hours, using antibodies that bind with LAM in the urine sample. The bound antigens cause a color change to indicate presence of TB.

The LAM ELISA test was 59% sensitive and 96% specific in one study. The test sensitivity increased as CD4 cell counts declined in HIV-positive people and was 85% in those with CD4 cell counts below 50 (Shah 2009). This inverse relation between LAM ELISA's sensitivity and CD4 cell count was seen in another study where test sensitivity reached 67% in those with fewer than 50 CD4 cells, but the sensitivity in people with CD4 cell counts higher than 100 was very low at 4% (Lawn 2009). The quantitative analysis of LAM using the Clearview test showed that a higher measure of LAM correlated with greater bacterial burden in sputum, with disseminated TB in the blood of HIV-positive people, and with lower CD4 counts (Shah 2010). A study in South Africa is comparing the utility of both Alere's LAM Clearview ELISA and its Determine LAM lateral flow tests to diagnose TB among people with HIV initiating antiretroviral therapy. Clearview TB ELISA is available commercially in the United States and may be brought to STAG-TB in 2013 (Baker 2011).

A meta-analysis of results obtained with the LAM ELISA test confirmed that though this noninvasive LAM assay may identify TB in HIV-positive people with severe immune suppression, its suboptimal sensitivity requires that the populations in which it can be used be defined carefully (Minion 2011).

3. Rapid Colorimetric Drug Susceptibility Testing

FIND and the London School of Hygiene and Tropical Medicine are studying the feasibility of a rapid colorimetric drug susceptibility testing (DST) method using thin layer agar (TLA) at microscopy centers. Colorimetric DST is conducted by culturing TB from sputum sample on a TLA plate that has four different colored quadrants, three of which contain isoniazid, rifampicin, and a quinolone. The plate is sealed after the sputum is transferred onto the plate, which obviates the need for rigorous biosafety precautions. The plate is then incubated; any growth causing a color change is examined under a microscope to confirm MTB. Results take two to three weeks (Sandarac 2011).

A systematic review and meta-analysis of three colorimetric DST studies using non-TLA methods showed that the method was 100% accurate for detecting rifampicin and isoniazid resistance, and the mean time to result was 11 days (Minion 2010). The TLA DST's sensitivity and specificity needs to be confirmed.

In Reference Laboratories

1. The GenoType® MTBDRsl

The WHO approved line probe assays (LPAs) for rapid diagnoses of MDR-TB in 2008. MDR-TB is resistant to two of the most powerful first-line TB drugs, rifampicin and isoniazid. The MTBDR*sl* test by Hain Lifescience is an LPA being developed to detect certain second-line TB drug resistance-associated genetic mutations. The test uses probes to detect gene mutations associated with resistance to fluoroquinolones (FQs); aminoglycosides/cyclic peptides including the injectable TB drugs amikacin, kanamycin, and capreomycin; and the first-line drug ethambutol. When used with the LPA for rifampicin and INH resistance, this test can identify extensively drug-resistant TB (XDR-TB) strains—MDR-TB strains also resistant to any FQ and at least one second-line injectable.

Peer-reviewed studies examined the test's ability to detect resistance to mutations in clinical isolates, but not on direct sputum samples. One such study showed the test to be sensitive in detecting FQ (75.6%) and kanamycin (100%) resistance and less so for ethambutol (64.2%). The specificity was 100% for all three drug classes (Kite 2010). Similar results from another study showed MTBDR*sl* sensitivity and specificity to be 87% and 96% for FQ, 100% and 100% for amikacin, 77% and 100% for kanamycin, 80% and 98% for capreomycin, and 57% and 92% for ethambutol respectively (Brosier 2010).

The rapid LPA to detect XDR-TB provides results in less than five hours, and can prevent inappropriate treatment with ineffective drugs to which the patient will not respond. In 2010 a WHO-convened expert group considered the MTBDR*sl* test but a decision on the test was postponed until further data are available on its performance using direct sputum samples. FIND and Hain Lifescience are gathering these data. STAG-TB may review the results in 2012.

2. The MTB MIC Plate

The US National Institutes of Health–funded TB Clinical Diagnostics Research Consortium (CDRC) and TREK Diagnostic Systems are collaborating to study the Sensititre® MTB MIC Plate. This test contains 12 first- and second-line anti-TB drugs in a single plate for the assessment of minimal inhibitory concentrations (MICs). The plate has a minimum of seven dilutions for each of 12 drugs. To detect drug-resistant TB the plates are inoculated with the TB isolates, sealed, and then incubated at 34–36 degrees Celsius for up to 21 days. Resistant strains are usually detected in ten days. The plate eliminates the need for each laboratory to create its own antibiotic dilutions as it contains standardized quality assured antibiotics at correct concentrations. This can avoid a major source of errors in conducting DST. The CDRC is studying the Sensititre MTB MIC Plate to assess the incremental improvement it can offer in identifying multidrug–resistant and extensively drug-resistant TB. WHO may review the results by 2013 (Dorman 2011; Sullivan 2010; TREK Diagnostic Systems 2011).

Recommendations

Resources for a Point-of-Care Test

The biggest unmet need in TB diagnostics is for a POC test. There is an urgent obligation to fully resource efforts 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.

To accelerate this progress, in February 2011 the Bill and Melinda Gates Foundation announced a new grant program, Biomarkers for the Diagnosis of Tuberculosis, which will provide up to US$12 million to identify host and/or pathogen biomarkers that can quickly identify TB disease in low-resource settings.

Biomarker discovery requires well-characterized samples from people with and without TB and at various stages of disease and cure so that candidates can be validated in specimens from a wide variety of patients. In 2010 the US Food and Drug

Administration provided funds to the TB Alliance to create a sample bank with the TB Trials Consortium and the AIDS Clinical Trials Group; the Consortium for TB Biomarkers (CBT^2) will bank samples collected from study participants, many of whom will be followed through the duration of the study and monitored for relapse. It will have well-characterized samples from different phases of TB disease and cure. Although this effort is focused on identifying surrogate biomarkers for treatment outcomes, the CBT^2 may provide opportunities for biomarker discovery work.

As the CBT^2 is being established, another sample bank at the WHO's Special Programme for Research and Training in Tropical Diseases (TDR) is in danger of being closed due to budget cuts. Instead of closing, sample banks need to expand and store a wider variety of samples in order to support the research required for the development of new diagnostics.

Ensuring That the Global TB Diagnostics Pipeline Includes All Developers

The current diagnostics pipeline of the New Diagnostics Working Group (NDWG) of the Stop TB Partnership does not include all TB diagnostics in development. There is an urgent need for the NDWG to conduct an independent and transparent assessment of TB diagnostics in the all stages of development using agreed-upon specifications. The WHO and the Stop TB Partnership need to facilitate new developers and funders entering the TB diagnostics field. The WHO should clarify data standards it requires a product to meet to pass an expert review and be recommended by STAG-TB.

Addressing Regulatory Gaps in TB Diagnostics

TB diagnostics are not well regulated, especially in high-TB-burden settings. This is demonstrated by the fact that commercial serological tests for TB antibody detection are available in 17 of 22 high-TB-burden countries, despite evidence of their poor performance and though no international guideline recommends their use. In India alone it is estimated that 1.5 million serological tests were done annually at a conservative cost estimate of US$15 million—most of which was borne by patients (Gernier 2011). 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% (World Health Organization 2008b). Based on these data the STAG-TB passed a negative recommendation on the use of commercial serological tests for TB in 2010 (Morris 2011; Steingart 2011; World Health Organization 2010a).

In 2010 the WHO recommended against the use of interferon gamma release assays to diagnose active or latent TB in low- and middle-income countries (World Health Organization 2010a).

Information about the WHO-recommended TB diagnostic tests and algorithms should be widely disseminated to educate all TB providers and civil society organizations to promote proper use of good tests and procedures and to prevent inappropriate use of inaccurate diagnostics (Specter 2010). 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 (Pai 2011).

Scaling Up WHO-Recommended Diagnostics in the Absence of Better Tests

Though an ideal TB diagnostic does not yet exist, the scale-up of recently recommended diagnostics could reduce disease burden among populations in greatest need for improved TB diagnostics.

1. Algorithms for the Identification of Smear-Negative and Extrapulmonary TB and to Rule Out Active TB in HIV-Positive Adults at the Peripheral Laboratory Level

The WHO has recommended several algorithms to diagnose and treat TB in people with HIV, a population in which TB is difficult to identify using the sputum smear test. There is growing evidence to support the scale-up of these algorithms for the identification of smear-negative and extrapulmonary TB in adults with HIV (World Health Organization 2007b, 2010b).

A South African study examined the use of the WHO algorithm to diagnose and provide rapid access to treatment for smear-negative TB in seriously ill people with HIV. The study showed that 83% of those whose access to treatment was managed with the WHO-recommended algorithm were alive eight weeks after admission compared to 68% of patients diagnosed and treated using standard practices (Holtz 2011). A study in Cambodia using the algorithm to diagnose TB in ambulatory HIV-positive people showed that the median time to treatment initiation was five days. The time to initiation was longest at nine days for smear-negative TB and shortest at two days for extrapulmonary TB. The sensitivity and specificity of the algorithm to diagnose smear-negative TB in people with HIV were 58.8% and 79.4%, respectively (Koole 2011).

A study that looked at the use of cough of any duration, fever, and night sweats to identify people with TB had concluded that the algorithm to screen out active TB should include a combination of all three symptoms rather than focus only on cough (Cain 2010). In 2010 the WHO developed a simple symptom-based screen to rule out risk of TB disease in people with HIV using current cough of any duration, night sweats, fever, or weight loss. A meta-analysis of observational studies had showed

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that using the absence of all of these four symptoms, the screen was able to accurately predict those without TB by 97.7% if the prevalence of TB in people with HIV was at 2%. The test's ability to predict absence of disease declined to 90% when TB prevalence was 20%. Because of its ability to rule out the presence of TB disease this symptom screen is recommended to identify people with HIV who don't have TB disease and can be given isoniazid preventative therapy (IPT) (Getahun 2011). Recent studies comparing 36 months of IPT to six months of IPT showed a 43% reduction of TB in people with HIV living in Botswana (Samandari 2011).

2. Xpert® MTB/RIF: A Recently Recommended TB and MDR-TB Diagnostic Test for the Peripheral Laboratory Level

In 2010, STAG-TB recommended the use of the Xpert MTB-RIF test—a rapid, automated NAAT that can diagnose TB and rifampicin resistance in two hours and does not require biosafety equipment or highly skilled laboratory workers. Because of its many advantageous specifications, the test can potentially be done at district health centers; however, it does need a consistent supply of electricity. Though it is shown to be cost-effective, its current price is US$17,000 for the machine and nearly US$17 per test (Roscigno 2010). These requirements will impede Xpert's rollout in many settings. The Xpert MTB-RIF test's overall sensitivity was 90.3% in all culture-confirmed TB and 76.9% in smear-negative cases. The specificity for the Xpert MTB-RIF test was 99%. For rifampicin resistance the Xpert test was 94.4% sensitive and 98.3% specific. The sensitivity of smear microscopy was lower than the Xpert MTB-RIF test at 67.1% and varied from 44.6% in people with HIV to 72.3% in people whose HIV status was negative or unknown.

Xpert MTB-RIF reduced time to TB detection to an average of zero days, compared with one day for microscopy, 30 days for solid culture, and 16 days for liquid culture. The time to initiate treatment for smear-negative TB was reduced from 56 days for smear-negative, culture-positive TB to five days for Xpert MTB-RIF. Although the Xpert MTB-RIF results did not inform initiation of MDR-TB treatment, the use of the test reduced time to detection of rifampicin resistance to one day, compared with 20 days for a line probe assay and 106 days for a culture DST. This study clarified the test could be run successfully on batteries; other factors like temperature and humidity still posed challenges. The manufacturer does not recommend the use of the test over 30 degrees Celsius, and the test cartridge stability requires the temperature to remain between 2 and 28 degrees Celsius. Dust and humidity caused a few breakdowns, but information was not available about the specifics of these failures and the subsequent cost or time to repair the machine. The company is devising methods to perform the annual calibration of the machine in the least disruptive manner (Boehme 2011).

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Since the first evaluation of Xpert MTB-RIF in 2010, at least 15 studies and articles have been published. The accumulating evidence clearly shows that the test outperforms sputum smears in everyone and especially in HIV-infected persons, and it reduces time to results and allows more rapid initiation of treatment. Studies are needed to examine its usefulness outside a district laboratory setting and examine its effect on improving treatment outcomes.

Disseminating Results of Diagnostics Scale-up to Strengthen TB Diagnostics Advocacy

The WHO and the Stop TB Partnership should work with the lead sponsor of a recommended diagnostic to track the rollout of recommended tools, facilitate coordination of its implementation, and gather operational and outcome data important to patients and programs. Documenting the lessons and successes of scale-up can inform advocacy for increased funding and highlight effective practices to expedite scale up effective diagnostics.

The WHO's Global Laboratory Initiative is creating a website to provide information on the uptake of the Xpert MTB-RIF test. This website will have data from partners implementing the test and track where it is being rolled out, who is providing funding, and how many tests are being performed. The website will collect information from the manufacturer to track challenges in scale-up and how these are being addressed.

Documenting the impact of effective diagnostics is essential to support advocacy to increase global funding for TB diagnostics, which in 2009 was a paltry US$41 million—far short of the US$340 million need estimated by the *Global Plan to Stop TB: 2011–2015* (Jiménez Salazar 2011).

Conclusion

After a burst of activity in the past four years, the pace of new diagnostics being brought to STAG-TB is slowing down, while there are major gaps in the availability of tools appropriate for use in all levels of the health system and especially at the health post level. Restoring a more robust pipeline requires a well-funded research agenda to develop biomarkers, technological platforms, and resources such as sample banks critical for the development of new diagnostics. Furthermore, a comprehensive and proactive strategy is needed to ensure that all diagnostic developers are contributing to the global TB diagnostics pipeline tracked by the NDWG.

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The Tuberculosis Treatment Pipeline

BY CLAIRE WINGFIELD

It has been over 50 years since rifampin (also referred to as rifampicin) was synthesized. It was the first compound from a new class of anti-tuberculosis drugs called rifamycins, and remains one of the most powerful in its class. Two more anti-TB rifamycins were subsequently developed—rifabutin and rifapentine—but no new classes of anti-TB drugs have been approved since then. The discovery and introduction of rifampin marked the end of a busy two decades in TB drug development. After the breakthroughs made between the 1940s and 1960s TB drug development languished until outbreaks of TB resistant to the most powerful TB drugs—isoniazid and rifampin—coincided with the rise of the HIV epidemic in the early 1990s. These events cast a harsh light on the flaws in current TB treatment strategies—long duration of treatment, high pill burden, side effects, and treatment adherence issues—and led to a resurgence of interest in developing better, simpler, and shorter treatment regimens.

Over the past decade the TB treatment pipeline has returned from near death. Six new compounds from existing and novel drug classes are being evaluated in clinical trials with more in preclinical studies. Existing drugs that have been used off-label to treat TB and other bacterial infections are being repurposed to shorten treatment duration, reduce adverse events, and improve treatment outcomes. Two compounds from novel drug classes may be considered for regulatory approval in the coming year. Despite this progress we must remain only cautiously optimistic because while the pipeline is the most promising it has been in decades, it is still insufficient to eliminate TB as public health threat.

Concerns about small profit margins have deterred many large pharmaceutical companies from investing in TB drug development. As a result the TB treatment research community is small and consistently underfunded, with only a handful of companies engaged. Public sector research institutions and academia conduct much of the basic science research to fill the pipeline and work with product developers to conduct clinical studies. But TB researchers are resilient and resourceful and, as this year's treatment chapter will show, they have done a lot with a little.

Latent TB Infection

Every one of the two billion persons who are latently infected with TB is a potential future case of TB disease. Therefore, treatment of latent TB infection (LTBI) is critical to reducing the pool of new cases. The World Health Organization (WHO) recommends six to 12 months of daily isoniazid—one of the backbone drugs of TB treatment—particularly for people with HIV and children who are five years of age and younger (World Health Organization 2010b). Isoniazid preventive therapy (IPT) has long been a controversial issue in TB control. There is a mountain of clinical evidence proving the effectiveness of IPT in preventing the progression of latent infection (when a person's immune system is able to control TB) to active disease (when a person is sick and able to transmit TB to others). But IPT is for healthy people, and therefore it is difficult to ensure treatment adherence. Ruling out active disease may be difficult if the patient is immunocompromised or has HIV and low CD4 counts. In many countries clear guidelines for programmatic implementation of IPT do not exist. Several large-scale studies are underway that attempt to gather evidence on how best to scale-up IPT in HIV-prevalent settings. Alternative preventive treatments which may be easier to adhere to or shorter in duration are being evaluated as potential replacements for IPT. See Table 1.

TABLE 1: LTBI studies as of July 2011

Study	Regimen	Duration of regimen	Sponsor	Study locations
PREVENT TB (study 26)	once-weekly rifapentine + isoniazid	12 weeks	TB Trials Consortium, Sanofi-Aventis	USA, Canada, Spain, Brazil
THRio—CREATE	daily isoniazid	6 months	Bill and Melinda Gates Foundation	Brazil
Thibela—CREATE	daily isoniazid	6 months	Bill and Melinda Gates Foundation	South Africa

Rifapentine has a long half-life, allowing for intermittent dosing, and has been shown to have superior bactericidal activity to rifampin and rifabutin (Heifets 1990). The TB Trials Consortium (TBTC), an international research network funded by the US Centers for Disease Control and Prevention (CDC), has been working with Sanofi-Aventis—the pharmaceutical company that makes rifapentine—to evaluate it in treatment-shortening regimens for LTBI and active disease.

The TBTC has been conducting TB treatment trials since the 1990s and recently completed the PREVENT TB trial—also referred to as TBTC study 26—which evaluated whether giving rifapentine with isoniazid can shorten LTBI treatment. The study com-

pared 12 weeks of once-weekly isoniazid and rifapentine to nine months of daily isoniazid. It showed that the rifapentine and isoniazid regimen was as effective as the standard self-administered nine-month daily regimen of isoniazid, and had better completion rates (Centers for Disease Control and Prevention 2011). Final safety data are pending for people with HIV and children between the ages of 2 and 12 years, and should be available by the end of 2011.

Because this study was conducted in low- and middle-TB-burden settings, further studies evaluating its effectiveness and tolerability in high-burden countries are needed—particularly those with high HIV prevalence. Each rifapentine and isoniazid dose was directly observed, so the recommendations for this regimen will include directly observed therapy (DOT) as the preferred method of administration. Recognizing that this is not ideal for all programs and patients, the TBTC is planning a study to compare adherence rates using DOT or self-administration with and without electronic reminders.

TB programs in low-burden countries like the United States—where much of TB control is geared toward treating LTBI—are already considering this 12-week regimen. The CDC is expected to issue interim recommendations for the use of this new regimen in the United States later this year. The potential for a once-weekly regimen with shortened duration may not only improve adherence but also be cost effective by reducing patient visits, staff time, and number of pills being taken. Whether this can be reproduced in high-burden countries is unknown until studies are conducted. Until there is more data IPT remains the best option for treating LTBI in high-TB-burden settings. Two major studies evaluating population level scale-up of IPT in high-HIV and -TB settings are nearing completion and have already strengthened roll-out of IPT in Brazil and South Africa.

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—is wrapping up two studies evaluating the impact of programmatic implementation of mass IPT on TB incidence. Final analysis from the THRio study, which evaluated the provision of IPT among HIV positive persons attending HIV clinics in Brazil, is completed and will be released in July 2011. The final data from the Thibela study, which evaluated mass, mineshaft-wide IPT in South African gold mines, will be released in 2012. Already both studies have led to changes in national guidelines and clinical practice.

In Brazil, CREATE study data were cited as the rationale for expanding integration of IPT with ART and placing responsibility for IPT on the national AIDS program (NAP). In late 2009, the NAP promulgated a policy requiring HIV clinics to take responsibility for screening patients for active TB and providing IPT to patients testing positive with a tuberculin skin test (TST). The NAP has included IPT and TB drugs in the SICLON, the system that controls drugs used to treat HIV and HIV-related op-

portunistic infections. This is an important step because it means that TB prevention and treatment will have the same status, availability, and control in HIV clinics nationwide as all the other medications (Eldred 2011). Likewise, in South Africa, the Thibela team gave substantial input into national department of health guidelines, making South Africa the first country to adopt the WHO's recommended four-symptom TB screening tool (Eldred 2011).

Isoniazid preventive therapy is widely recognized as the standard of care for treating LTBI, but it is not an option for people who are latently infected with drug-resistant TB (DR-TB). Treatment of close contacts of DR-TB cases is usually based on anecdotal evidence and drug availability. The AIDS Clinical Trials Group (ACTG)—a research network that is funded by the US National Institutes for Health (NIH)—and the TBTC are considering a study that would evaluate the efficacy and tolerability of TMC207 (bedaquiline) compared with INH. ACTG study 5300 will compare TMC207 to INH for preventing TB disease in those 13 years and older who have household contact with persons with confirmed DR-TB. A number of factors must be addressed before this study can start, including approval from the company to begin to study the compound for this purpose before it is approved for treatment of active TB. It is promising that DR-TB is finally being considered as critical to LTBI clinical research.

Active Disease

Current standard treatment for drug-susceptible TB (DS-TB)—TB bacteria susceptible to all first-line drugs—has shown a 95% cure rate. Unfortunately, many TB programs are understaffed and poorly funded, therefore the majority of TB patients access care in settings that are vastly different from the tightly controlled environment of a research study. Actual cure rates can be as low as 57% in some high-burden countries (World Health Organization 2010a). The standard of care for DS-TB is two months of a four-drug combination—isoniazid, rifampin, ethambutol, and pyrazinamide—followed by four months of a isonizid and rifampin (or 2HRZE/4HR). This six-month regimen requires daily dosing and is often given as DOT, which is labor-intensive for both patient and provider. A number of studies underway are using existing compounds to reduce the length of first-line treatment to improve adherence rates.

TABLE 2: Existing TB drugs in clinical studies for DS-TB as of July 2011

Study	Drug(s)	Drug class	Sponsor	Phase	Status
TBTC study 29X	rifapentine	rifamycin	TBTC/Sanofi-Avenits	Phase II	Enrolling
Rifaquin	rifapentine + moxifloxacin	rifamycin + flouroquinolone	British MRC and EDCTP	Phase III	Enrolling
REMox	moxifloxacin	flouroquinolone	TB Alliance, Bayer, British MRC, and University College London	Phase III	Enrolling
OFLOTUB	gatifloxacin	flouroquinolone	OFLOTUB and TDR	Phase III	Completed; final results pending

Repurposing Existing Compounds

Drug-susceptible TB

The TBTC has been evaluating the antimicrobial activity and safety of daily rifapentine for potential future use in treatment-shortening regimens. The TBTC's study 29 evaluated the use of rifapentine 600mg given five days a week in place of rifampin in the context of standard therapy with isoniazid, pyrazinamide, and ethambutol during the eight-week intensive phase of first-line TB treatment. The study found no significant difference in the efficacy between the two regimens, whether defined as culture conversion rates at eight weeks (the primary endpoint) or time to culture conversion. Rifapentine administered according to the study protocol was safe and well tolerated. A notable finding in the study was that African site volunteers had lower concentrations of rifapentine compared to non–African site volunteers despite receiving the same dosages of the study drug. This is not fully understood, but may be partly due to the enhancing effect of food consumption on rifapentine concentrations. African patients in study 29 had fasted before taking rifapentine. The low rifapentine concentrations may also be due to pharmocogenomic differences—influence of genetic variation on drug response—between African and non-African participants, but further studies are needed to confirm this. The TBTC will be conducting a double-blind dose-ranging study in patients with drug-susceptible pulmonary tuberculosis to determine the safety and tolerability of rifapentine taken at 10 mg/kg, 15 mg/kg, or 20 mg/kg with food for seven days a week during the intensive phase of therapy.

Several studies underway are using flouroquinolones to shorten the duration of treatment from six to four months. Flouroquinolones are a class of broad-based antibiotics used to treat many bacterial infections. They have been used as part of second-line treatment for multidrug-resistant TB (MDR-TB) but are not licensed for TB. The drugs in this class—levofloxacin, ofloxacin, moxifloxacin, and gatfloxacin—are completely cross resistant to one another.

The Rifaquin study—being conducted by the British Medical Research Council (MRC) with funding from the European and Developing Countries Clinical Trials Partnership (EDCTP)—is assessing whether rifapentine and moxifloxacin, when given together, can shorten first-line treatment and allow for intermittent dosing. It is a three arm study comparing the six-month standard-of-care regimen (2HRZE/4HR), versus two months of daily ethambutol, rifampin, and pyrazinamide plus moxifloxacin followed by two months of twice-weekly moxifloxacin and rifapentine ($2EMRZ/2P_2M_2$), versus two months of daily ethambutol, moxifloxacin, rifampicin, and pyrazinamide followed by four months of once-weekly moxifloxacin and rifapentine ($2EMRZ/4P_1M_1$). Recruitment is ongoing.

The Global Alliance for TB Drug Development (TB Alliance) is conducting the REMox TB trial in collaboration with University College London and the British MRC as part of its moxifloxacin for TB development program with Bayer Healthcare. The trial is receiving major funding from the Bill and Melinda Gates Foundation, the EDCTP, and USAID and through the NIH which will be enrolling volunteers through the ACTG. This phase III trial is evaluating the use of moxifloxacin in place of ethambutol or isoniazid to shorten first-line treatment to four months. The study is currently enrolling in Africa, Asia, and Latin America, and is in the process of additional sites. Enrollment will be complete by the end of 2011, with final study results by 2014 (Ginsberg 2011).

Patient follow-up has been completed in the OFLOTUB consortium's trial evaluating gatifloxacin as a replacement for ethambutol in a shortened first-line treatment regimen. Problems in data management have resulted in unexpected delays in data analysis. Safety and efficacy results are expected by the end of 2011 (Lienhardt 2011).

While it is encouraging to see so much research underway to improve treatment for DS-TB, children are absent from all of these studies. While effictiveness in children may be extrapolated from adults, safety and proper dosing cannot. But children are more susceptible than adults to rapid progression from exposure to infection and to severe disease. Therefore safety, tolerability and pharmacokinetic (PK) data—how a drug is absorbed, distributed, metabolized, and eliminated by the body—must be collected to establish safety profile and accurate dosing in children of all ages and development stages.

Pediatrics

Children have been excluded from TB treatment research for the most part and are not a priority for national TB programs. Because of the difficulty in confirming a TB diagnosis in children using bacteriological methods such as sputum smear microscopy or culture, researchers and product developers are hesitant to conduct studies in children. Likewise, the focus on smear-positive TB, which is more contagious, means public health programs often neglect young and HIV-infected children. There are considerable differences in national recommendations in pediatric drug dosing (Ramachandran 2011), and many children have been receiving sub-therapeutic levels of TB drugs. In 2010 the WHO issued *Rapid Advice: Treatment of Tuberculosis in Children* to provide a framework for accurate dosing of first-line treatments for children (World Health Organization 2010c). Literature reviews of PK and toxicity data in children have shown that, while the principles of treatment in children and adults are the same, the dosages are not (Graham 2010). Children metabolize drugs differently, and therefore the amount of drug given to them cannot just be scaled down from adult data (Ramachandran 2011).

The 2010 WHO guidelines recommend new dosages of isoniazid, rifampin, pyrazinamide, and ethambutol to account for these differences. Unfortunately, implementing these new recommendations is quite challenging for national programs because the child-friendly formulations (e.g. crushable, dispersable, or scored tablets or capsules) of current single-dose drugs and fixed-dose combinations (FDCs) that are meant to ease dosing of multidrug regimens do not exist. Inclusion of children earlier in treatment research with prioritization of collecting PK and safety data is essential to the development of child-friendly treatment regimens for first- and second-line drugs. As a matter of urgency simple weight-band tables that can guide the dosages and schedules for single and combinations of current drugs like those used in pediatric ARV treatment are needed.

TABLE 3: Existing TB drugs in clinical studies for DS-TB as of July 2011

Study	Description	Sponsor	Phase	Status
STREAM	Efficacy and safety of 9-month, 7-drug regimen	IUATLD /BritishMRC	Phase III	Enrollment pending
LiMiT	Safety and tolerability of low-dose linezolid	TBTC	Phase II	Completed

MDR-TB Treatment

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) tria. It will assess a nine-month standardized treatment regimen for MDR-TB that achieved excellent outcomes with a cure rate of 87% in a non-randomized observational study in Bangladesh (Van Deun 2010). Modeled on the Bangladesh regimen, the STREAM regimen uses moxifloxacin, clofazimine, ethambutol, and pyrazinamide for nine months, supplemented by prothionamide, kanamycin, and isoniazid during an intensive phase of four months. 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 British MRC is conducting this trial and is expected to begin enrollment in several sites in late 2011 and early 2012 (Ornstein 2011).

Last year's report included a description of the TBTC's LiMiT study (also known as study 30), a double-blind, placebo-controlled trial evaluating the safety and tolerability of low-dose, limited-duration linezolid—an oxazolidinone used off-label in treatment of DR-TB. The study closed enrollment in April 2010 and completed follow-up in September. Unfortunately, conclusions regarding the safety and tolerability of lower-dose linezolid will be limited because the investigators found evidence of sporadic, nonrandom irregularities in the distribution of the study drug to patients not in keeping with their treatment assignment. Failure to implement the protocol correctly jeopardizes the validity of study data. The research team and TBTC are committed to additional analysis furthering the understanding of what happened and in sharing such knowledge with the broader research community.

Maternal TB

TB control is crucial to maternal and child health in TB-endemic areas. TB is the leading infectious cause of death in women (Gupta 2011).Women bear the greatest burden of HIV during their childbearing years, and the same applies to TB. Maternal TB/HIV coinfection is associated with high incidence of postpartum maternal and infant death (Gupta 2007) and increased risk of maternal transmission of HIV and TB (Gupta 2011; Mofenson & Laughton 2007). Yet there is a dearth of data guiding how to treat pregnant women with TB drugs. A recent observational study conducted in Iran followed six pregnant women diagnosed with MDR-TB and found that treatment with a standardized second-line regimen was safe and effective in curing maternal TB and preventing childhood TB (Tabarsi 2010). These results are encouraging, but only six volunteers participated in this study, so the findings are not generalizable. Many second-line drugs have not been evaluated during pregnancy and the evidence is weak for those—such as linezolid and streptomycin—contraindicated for use in this population. While conducting clinical trials in pregnant women may be challenging, it is imperative that research institutions and product developers conduct PK and safety studies in them to ensure that these drugs are used safely and effectively to prevent and cure maternal and childhood TB.

Novel and Second-generation Compounds

The *Global Plan to Stop TB 2011–2015* estimates that US$700 million annually is needed to adequately fund TB treatment research over the next five years (Stop TB Partnership 2010). To reach this target, 2011 funding levels must more than triple. With the current global fiscal crisis, and with budget cuts looming for public-sector funders, it seems unlikely that this will happen. But as new compounds move through the pipeline private-sector investment is increasing. Just by continuing a phase II study of its new compound, Otsuka Pharmaceuticals became the leading funder of TB treatment research in 2009 (Jiménez Salazar 2011). For the first time in decades there are promising drugs with novel mechanisms of action that may be considered for regulatory approval in the next year. These new drugs may revolutionize TB treatment in the not-so-distant future. See Table 4.

TABLE 4: Novel and second-generation compounds as of July 2011

Agent	Class	Sponsor	Status	Indication
AZD5847*	Oxazolidinone	AstraZeneca	Phase I	TBA
PNU-100480	Oxazolidinone	Pfizer	Phase I	DR-TB
SQ 109	Diamine	Sequella/PanACEA	Phases I/II	DS-TB/DR-TB
PA-824	Nitroimidazole*	TB Alliance	Phases II	DS-TB
OPC-67683 (delamanid)	Nitroimidazole*	Otsuka	Phase II	DR-TB
TMC207 (bedaquiline)	Diarylquinolone*	TB Alliance/Tibotec	Phase I	DS-TB
		Tibotec	Phase II	DR-TB

Notes: *Indicates new drug class.

AZD5847

AstraZeneca Pharmaceuticals has completed two phase I safety, tolerability, and PK dose-escalation studies in healthy volunteers for its second-generation oxazolididnone, AZD5847. Proof of principle was demonstrated, since plasma concentrations exceeded the therapeutic exposures predicted by preclinical models at doses that are generally well tolerated. The detailed results will be presented in fall 2011. The compound will be moving into a phase IIa 14-day extended and early bactericidal activity (EBA) study in volunteers with DS-TB (Lawrence 2011).

PNU-100480

A multidose study of Pfizer's second-generation oxazolidinone PNU-100480 in healthy volunteers found all doses of PNU-100480 (up to 600mg twice per day) to be safe and well-tolerated and that they exhibited superior bactericidal activity to linezolid—an earlier-generation oxazolidinone used as last resort drug for DR-TB. The first study in TB patients is anticipated to begin enrollment in June 2011. Pfizer intends to develop the compound for DR-TB (Wallis 2011).

SQ109

SQ109, a second-generation ethane diamine antibiotic, is the lead compound from Sequella. With collaborators from the Pan African Consortium for Evaluating Anti-tuberculosis Agents (PanACEA), Sequella is evaluating SQ109 in a phase IIa early bactericidal study to determine optimal dosing in DS-TB. Phase II/III studies are expected to begin enrollment in 2012. In parallel, Sequella and the Maxwell Biotech Venture

Fund announced an agreement to develop SQ109 for DR- TB in Russia, Armenia, Azerbaijan, Belarus, Kazakhstan, Kyrgyzstan, Moldova, Tajikstan, Uzbekistan, and possibly Turkmenistan and Ukraine. (Horwith 2011).

Regulatory Challenges

Regulatory rules and requirements vary from country to country or region. Approval from stringent regulatory authorities like the US Food and Drug Administration (FDA) or the European Medicines Agency (EMA) has traditionally been sufficient for countries with limited regulatory capacity to grant approval for new treatments, particularly for life-threatening conditions. However, there is limited regulatory experience in the TB field because no new drug class has been approved since the 1960s and regulatory science is much more demanding now than it was then. Requirements for regulatory approval for TB treatments are not harmonized across agencies; for instance, the EMA requires that drug developers submit a pediatric investigational plan and timeline for evaluating a new TB compound in children while the FDA does not. The lack of regulatory harmonization means sequential and/or parallel regulatory filings in high- and low-burden countries along with long review timelines and individual application requirements (Haaxaire-Theeuwes 2011). Even applying to conduct a study in a country may take up to one year to get a clinical trial approved. These administrative delays hinder implementation and raise the cost of studies, and may deter companies from investing in developing treatments for TB.

PA-824

PA-824 comes from a new class of drugs knows as nitroimidazoles, and is licensed by the TB Alliance from the former biotech company Chiron. PA-824 has been tested in two extended, dose-ranging EBA trials assessing the ability of doses from 50mg to 1200mg given daily for 14 days to kill TB in the lungs of newly diagnosed patients. Based on the results of these studies, a 200mg dose of PA-824 was selected for late-stage development as one component of a novel regimen to be tested for treatment of both DS- and DR-TB. Results from the first study were published in 2010. The results of the second EBA study will be published later in 2011 (Ginsberg 2011).

OPC67683 (delamanid)

Delamanid, formerly known as OPC67683, comes from the same class of drugs as PA-824; the two drugs are completely cross resistant to one another. Otsuka Pharmaceuticals is in the process of completing its analyses of data from a phase IIb study of

delamanid plus optimized background therapy in volunteers with confirmed MDR-TB as well as drug-drug interaction (DDI) studies with ARVs. Plans for future clinical trials will follow the completion of the analysis of these trials. Delamanid neither induces nor suppresses the cytochrome P450 (CYP P450) enzymatic pathways; therefore, additional DDI studies are not planned in the near future. There are no plans for early or expanded access to delamanid until after the analyses of existing studies are complete (Carlevaro 2011).

Recently the company established Otsuka S.A., in Geneva, Switzerland, a new entity and subsidiary of Otuska Pharmaceuticals, which will serve as the company's central operations for developing and implementing public health policies regarding access and capacity building, and corporate social responsibility programs, in connection with its global TB program. This commendable development suggests Otsuka is sensitive to the global issues posed by the likely advent of a new TB drug.

TMC207 (bedaquiline)

Tibotec (a subsidiary of Johnson & Johnson) has developed TMC207—recently given the generic name of bedaquiline—the first compound from a new class of drugs called diarylquinolones. Final 24-week data from stage 2 of a phase II trial showed volunteers who added TMC207 to a standard background MDR-TB regimen had faster time to culture conversion and a higher number of culture conversions than in volunteers on standard MDR-TB treatment (McNeeley 2010). Stage 2 patients are being followed while they complete their background regimens.

The company is conducting DDI studies with ARVs known to inhibit CYP450. Coadministration with the boosted protease inhibitor lopinavir/ritonavir (LPV/r) increased exposure to TMC207 by approximately 20%. (van Heeswijk 2010). Results of the nevirapine interaction trial will be released in July 2011. ADDI study of TMC207 and efavirenz has been completed; final analysis is expected in mid-2011 (Dooley 2011).

Tibotec has finished recruitment at sites in Europe, Asia, and Africa for an open-label trial of TMC207. Adults with smear-positive, confirmed MDR-TB or extensively drug resistant TB (XDR-TB) are eligible, including people with HIV. Data will be available later in 2011. The company is currently in discussions with health authorities on the design of a phase III trial, planned to start in 2012. The pediatric investigational plan that will guide future clinical studies of TMC207 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 (Haaxaire-Theeuwes 2011).

The TBTC and the NIH-funded IMPAACT network are hoping to collaborate with Tibotec to conduct a PK study of TMC207 in children of all ages. The trial would start

with adolescents and work down to infants from birth to six months of age. Once data from HIV-positive adults become available, children with HIV would be included (Hessling 2011). This is contingent upon approval from Tibotec to use TMC207 preapproval.

Preapproval Access to Compounds

Expanded access and compassionate use programs provide preregulatory-approval access to lifesaving treatments—like ARVs—that have demonstrated efficacy to patients who cannot participate in a controlled clinical trial. These programs have been used to accelerate access to promising treatments for HIV and cancer but have never been implemented in the context of TB treatment. As promising new treatments for DR-TB advance through the pipeline it is important to provide access to them for people with limited to no treatment options—particularly people with XDR- or pre-XDR-TB. Between the submission of an application for regulatory approval and receiving it, the experimental drug is not accessible—regardless of the effectiveness of the drug—unless it is made available through an expanded access or compassionate use program. One of the concerns about providing preapproval access to drugs is how to ensure that they are used properly so that resistance doesn't develop to the drugs before they are made available to the general public. Some countries do not have a legal framework for compassionate use and therefore do not allow access to unlicensed drugs. Tibotec is the first company to provide access to its compound preapproval, and has initiated a compassionate use program to provide access to TMC207 to XDR- or pre-XDR-TB patients who are ineligible to participate in any other TMC207 study. This program is currently reviewing the first requests from health care providers. An expanded access trial is expected to begin in summer 2011.

Tibotec and TB Alliance are codeveloping TMC207 with Tibotec taking the lead for DR-TB, the TB Alliance taking the lead for DS-TB and the two organizations collaborating to discover "next generation" diarylquinolines—the same drug class as TMC207. The TB Alliance conducted a DDI study with TMC207 and rifapentine and rifampin this year. Results are expected to be published in 2011. The TB Alliance in collaboration with the ACTG are planning a DDI study with rifabutin to determine the optimal approach for moving forward with a rifamyacin-based TMC207 regimen for DS-TB. Preliminary results from a 14-day EBA study indicate that all TMC207 dosing regimens evaluated were well tolerated and produced measurable bactericidal activity. Final results of this study will be available in late 2011. Both PA-824 and TMC207 are being developed by the TB Alliance as part of combination regimens rather than single drugs (Ginsberg 2011).

Regimen Change

Although a combination of drugs is required to cure TB, drug development has traditionally evaluated one new compound at a time by adding an experimental drug to a standardized regimen. The FDA has expressed concern that this model of drug development is unethical given the risk for the emergence of resistance and rendering the new compound ineffective (Woodcock 2011), and has drafted *Guidance for Industry Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination* (Food and Drug Adminitsration 2010) to facilitate the development of novel combination therapies rather than sequential drug development. The Critical Path to TB Regimen (CPTR) was established in 2009 to provide a forum for different stakeholders in TB research to work together to speed up the development of novel TB regimens. There are several challenges to this approach, not limited to different timelines of drug development, the hesitation of sponsors to work together and share data, and the lack of appropriate drug-drug interaction data to guide dosing regimens in such studies. But these challenges are not insurmountable and if successful these types of studies could reduce the time to regimen change from over 20 years to less than 10 years.

TABLE 5: Regimen change as of July 2011

Study	Regimen	Sponsor	Phase	Indication
NC-001	PA824, moxifloxacin, pyrazinamide	TB Alliance	Phase II	DS-TB/DR-TB

NC-001

The TB Alliance has initiated the first novel TB treatment combination trial, NC-001. The primary objective of this trial is to evaluate the extended EBA, safety, tolerability, and PK of TMC207 alone, TMC207 plus pyrazinamide, PA-824 plus pyrazinamide, and PA-824 plus pyrazinamide and moxifloxacin, dosed daily over 14 days. PA-824 plus pyrazinamide and TMC207 plus pyrazinamide are promising building blocks for novel treatment-shortening regimens as they have been shown to be synergistic in a mouse model of TB. TMC207 plus PA-824, a combination that shows some antagonism in the same mouse model, is also being studied in NC-001 to evaluate whether it has potential in humans as a building block for a novel TB regimen for both DS- and DR-TB (Ginsberg 2011).

NC-001, initiated in early 2011, represents the first study in TB patients of a combination containing more than one new drug for TB; the novel three-drug regimen is PA-824 plus moxifloxacin and pyrazinamide. Enrollment into NC-001 has recently been completed. Results from this study are expected to be available by the end of 2011. Depending on the results of NC-001, a two-month treatment study of this three-drug regimen is being planned for initiation in early 2012 (Ginsberg 2011).

Recommendations

Current treatment strategies cannot eliminate TB as a public health threat by 2050. Treatment for active TB disease takes from six months to two years, requires patients to take multiple pills (in some cases at different times of day), and causes mild to severe (and potentially irreversible) side effects. Better drugs are needed, as are more data on how best to use current treatments in people with HIV and children who are at greater risk for disease progression and more severe disease.

Childhood TB

More than half of the ARVs approved to treat HIV have established simple weight band tables with pediatric dosing ranges and child-friendly formulations (Food and Drug Administration 2011). Meanwhile, there is a dearth of evidence guiding TB treatment for children (Burman 2008). Infants and young children bear a higher risk for TB disease progression. Pharmocokinetic and tolerability studies in children of all ages are desperately needed for current second-line drugs and new compounds in development. Once adult efficacy data has been established, pediatric PK and safety studies should be initiated to establish the optimal dose in children of all ages, starting with adolescents and then scaled down to infants. Likewise, manufacturers need to prioritize the development of FDCs and child-friendly formulations of current first-line and second-line drugs and new compounds for children. Without these formulations, the revised pediatric dosages will not be implemented and children will be denied the potential benefits of promising new drugs and regimens.

Maternal TB

TB remains a leading cause of death of women of childbearing age, yet few research institutions, product developers, and funders have prioritized this population. Maternal TB has a significant impact on the TB status and overall health of an infant. A pregnant woman who is coinfected with TB/HIV is 2.5 times more likely to transmit HIV to her newborn (Gupta 2011). If her TB remains untreated she is at risk for transmitting TB to her child in utero, during birth, or postpartum. It is imperative that mothers and their children be prioritized and included in TB treatment research.

Antiretroviral Therapy as TB Prevention

There are limited data on interactions between TB drugs and ARVs. Evidence continues to show the significant impact that ART has on reducing incidence and severity of TB among people with HIV, but there is very little information on how best to use current TB treatments and newer compounds with ARVs. Provision of ART is a critical intervention in preventing TB among people with HIV. Unfortunately, many people start ART at low CD4 counts, lessening the potential benefits from ART as TB prevention (Lawn 2011). Antiretroviral therapy must be scaled up in high-TB burden settings, and DDI studies with ARVs and new TB compounds are required to ensure that ART is included as an essential component of TB care.

Regulatory Requirements

Regulatory authorities need to provide clear guidance to drug developers on requirements for conducting clinical trials, providing preapproval access to promising compounds, and applying for licensure. These requirements should be harmonized or at least synergized as much as possible with other national regulatory agencies to avoid unnecessary delays, added costs, and missed opportunities for accessing lifesaving treatments.

TB Control

Cure rates for drug-susceptible TB may reach 95% in the best-functioning health systems, but the majority of TB patients are accessing their care in resource-limited settings where drug stockouts are not uncommon, not all drugs are quality assured, and staff are overwhelmed by the patient load and unable to provide adequate adherence support. As a result, many patients may find themselves relapsing or failing treatment because they did not complete their regimen or were not given the appropriate treatment. Countries need to commit to providing a consistent supply of quality-assured first- and second-line drugs and invest in developing and sustaining human resources required to run a functioning TB program.

Conclusion

Over the past decade, TB treatment research has seen greater investment from the public and private sector and has produced a number of promising advances. But more investment is needed to ensure that we are able to build on this foundation and revolutionize treatment of TB. Major funders like the NIH, the Bill and Melinda Gates Foundation, and pharmaceutical companies must not scale back on their contributions, and high-burden countries like Brazil, India, Russia, China and South Africa must increase their

investments. The potential to shorten treatment and dramatically improve outcomes for latent TB infection and active disease is close and demands commitments be kept and innovation encouraged if TB is going to be curable for all people.

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The Tuberculosis Vaccine Pipeline

BY CLAIRE WINGFIELD AND RICHARD JEFFERYS

The Bacille Calmette-Guérin (BCG) vaccine provides protection from the most severe forms of pediatric tuberculosis (TB) disease, saving the lives of an estimated 40,000 children each year. BCG is a valuable tool in combating child morbidity and mortality and is included in the World Health Organization (WHO) Expanded Programme on Immunization (EPI), but it is not sufficient to eliminate TB as a public health threat because it offers incomplete protection. Most important, BCG cannot prevent pulmonary TB—the most common form of the disease—and it is not recommended for use in HIV-positive infants because it can cause a potentially deadly immune reaction. A vaccine to provide lifetime protection against all forms of TB in all populations will be essential in eliminating TB. A novel vaccine that is only 60% effective could reduce TB incidence approximately 80% by 2050 (Abu-Raddad 2009).

TB vaccine development is resource- and time-intensive. Because vaccine studies must show that they are able to reduce TB incidence on a population level they take longer and require many more participants than do treatment and diagnostic trials. The search for a new TB vaccine has been excruciatingly slow despite the desperate global need, but recent developments offer encouraging signs of progress. Ten novel vaccine candidates are in clinical trials and there is a robust pipeline of constructs in preclinical studies thanks to the efforts of a relatively small but committed community of researchers, funders, and advocates.

Who Is Involved in Developing New TB Vaccines?

A handful of nongovernmental organizations, universities, and research institutions from the public and private sector are driving TB vaccine development. The South African TB Vaccine Initiative (SATVI), the European and Developing Countries Clinical Trials Partnership (EDCTP), the Tuberculosis Vaccine Initiative (TBVI), and Aeras are playing key roles in almost every TB vaccine trial. This reveals the limited infrastructure available for clinical TB vaccine research. SATVI is the only institution that currently has the expertise and capacity to conduct large-scale phase III efficacy studies and recently completed enrollment of the first efficacy trial in infants in more than 80 years. The EDCTP is playing a key role in facilitating TB vaccine research by

establishing "networks of excellence." The TBVI and Aeras are advocating for increased resources and working with regulators to clarify the pathway for a new vaccine. Each of these organizations is working to build TB vaccine research infrastructure but all remain underresourced in comparison to the needs they are attempting to address. A combination of large pharmaceutical and smaller biotechnology companies, universities and government institutions are conducting the basic science and clinical research that keeps the pipeline filled and moves existing candidates forward.

The Vaccine Clinical Pipeline

Ten vaccine candidates are currently being evaluated in phase I and II clinical trials. Although as of June 2011 twelve constructs are listed in the Working Group on New TB Vaccines' pipeline, one is inactive (*M. smegmatis*), and a phase III study of *M. vaccae* has been completed but studies results must be confirmed and yet no further studies of the vaccine are planned at this time.

TABLE 1. TB vaccine constructs in phase II clinical trials (as of July 2011)

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	GSK Biologicals, Aeras	Phase II
RUTI	Immunotherapeutic	Fragmented MTB	Archivel Farma	Phase II

MVA85A/Aeras 485

MVA85A/AERAS-485—a recombinant attenuated version of the vaccinia virus (cowpox) combined with TB antigen 85A—is the most clinically advanced TB vaccine to date. The vaccine 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.

A total of twelve clinical trials of MVA85A/AERAS-485 have been completed and four are ongoing. Phase I and II safety studies indicate that the vaccine is well tolerated, with no serious adverse events. A trial in infants given the vaccines recommended in the WHO EPI showed no negative impact, but the EPI vaccines did slightly reduce the magnitude of the immune responses induced by MVA85A. Researchers think that this may be because

the adjuvants—substances that stimulate an immune response to antigens in the vaccine—used in the EPI vaccines preferentially enhance the antibody Th2 immune response and thereby diminish the cellular Th1 response favored by MVA85A (McShane 2010). 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 is due to begin later this year (Woolley 2011).

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 is one of two adenoviral-vectored vaccines in the TB vaccine pipeline. The vaccine is a replication-deficient adenovirus 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. Adenoviruses are potent inducers of CD8 T-cell responses, which are considered important for developing an effective vaccine-induced immune response. This construct is being developed by Aeras and Crucell NV—a Dutch biopharmaceutical company with a particular focus on developing adenovirus-based vaccine vectors for infectious diseases.

When given after priming with BCG in adults, AERAS-402/Crucell Ad35 has been shown to induce polyfunctional CD4 T-cells and strong CD8 T-cell responses, suggesting it may have potential as an immunotherapy (Sadoff 2010). A phase II 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 (ClinicalTrials.gov 2011d). A phase II trial evaluating the safety and immunogenecity of AERAS-402/Crucell Ad35 in HIV-infected, BCG-vaccinated adults with greater than 350 CD4 cells was initiated in 2009. It is currently paused to further enrollment pending funding considerations (Leadman 2011).

GSK M72

GlaxoSmithKline (GSK) is working with Aeras to conduct phase II studies of GSK M72, a recombinant protein vaccine with an adjuvant. Early results show that the vaccine is well tolerated clinically and produces a measurable immune response. The vaccine has been studied with several of GSK's proprietary adjuvants, with a compound named AS01E eventually selected for further development. GSK M72 is a vaccine that is made up of an adjuvant and two recombinant TB proteins meant to strengthen the immune response to

two fragments of the TB bacterium that are commonly recognized by the immune system. The vaccine has induced robust polyfunctional CD4 cell responses against the M72 antigen, but no CD8 cell responses. No serious adverse events have occurred; the main side effects are transient local injection site reactions (Ofori-Anyinam 2010). A phase II study assessing the safety and immunogenicity in HIV-positive adults with or without ART in TB endemic areas is underway (ClinicalTrials.gov 2011c).

RUTI

RUTI is a killed TB vaccine that was originally discovered at Institut Germans Trias i Pujol and is 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 (Ruiz 2010). The WHO recommends six months of daily isoniazid as a standard of care to treat latent TB infection and prevent progression to active TB disease. The preclinical data suggest that the RUTI vaccine plus isoniazid for one month may be as effective as six months of isoniazid (Churchyard 2010). A phase II study that compared three different doses of RUTI plus one month of isoniazid to six months of isoniazid plus placebo in HIV-positive and HIV-negative adults has been completed (ClinicalTrials.gov 2011a). Final results are pending. If this regimen proves to be as effective as the standard of care for latent TB infection it might be preferable for TB programs because of the reduction in duration of therapy and potential for reduced risk of isoniazid resistance.

TABLE 2. TB vaccine constructs in phase I clinical trials (as of July 2011)

Agent	Strategy	Type	Sponsors	Status
HyVac4/AERAS 404 (SSI/SP H4-IC31®)	Prime boost	Recombinant protein	SSI, Aeras, Sanofi Pasteur, Intercell	Phase I
Hybrid-1+IC-31	Prime boost	Recombinant protein	SSI, TBVI, Intercell	Phase I
Hybrid-1+CAF01	Prime boost	Recombinant protein	SSI	Phase I
VPM1002	Prime	Recombinant live	Vakzine Projekt, Max Planck, TBVI	Phase Ib
Ad5Ag85A	Prime boost	Viral vector	McMaster university	Phase I
AERAS-422 (rBCG)	Prime	Recombinant live	Aeras	Phase I

HyVac4/AERAS 404, Hybrid-I+IC-31, Hybrid-I+CAF01, and SSI H56-IC31®

The Statens Serum Institute (SSI), a Danish research institution, has discovered key antigens and developed a number of technologies that are important for the development and production of a new TB vaccine. The SSI currently has three subunit protein vaccines combined with adjuvants in human testing: HyVac4/Aeras 404, Hybrid-I+IC-31, and Hybrid-I+CAF01. The SSI is partnering with Aeras, TBVI, Intercell (a biotech company), and Sanofi Pasteur (the vaccine division of the pharmaceutical company Sanofi-Aventis) to develop these constructs.

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 to stimulate T-cell mediated immunity. Aeras and the SSI entered into a development partnership for H4-IC31 in 2005. In 2008, the SSI partnered with Sanofi Pasteur to further develop this candidate. It has undergone three phase I clinical trials in adults and Aeras is currently conducting a phase I trial to test this candidate in healthy adults (Leadman 2011).

Hybrid1, containing the TB antigens 85B and ESAT6, is combined with either IC31 or CAF01 adjuvants (Hoff 2010). All are being developed as booster vaccines and have completed safety studies in humans.

SSI has published promising preclinical data on an additional candidate that include a novel latency-associated TB antigen, Rv2660c, along with Ag85B, ESAT-6 and the IC31 adjuvant (Aagaard 2011). Dubbed SSI H56-IC31®, this vaccine is now poised to undergo phase I testing in humans in a collaboration with Aeras supported by the Bill and Melinda Gates Foundation Grand Challenge #12 (GC#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 induced TB-specific immune responses, and is being developed as a priming vaccine (Grode 2010). A phase Ib trial is currently underway that evaluates safety, tolerability, and immunogenicity of three doses of VPM1002 in healthy adults using standard BCG immunization as a comparator (ClinicalTrials.gov 2011b).

Ad5Ag85A

Ad5Ag85A is the other adenoviral-vectored vaccine in the pipeline, and uses adenovirus 5 (Ad5). It is being evaluated as a BCG prime/boost vaccine. The developers at McMaster University are interested in pursuing intranasal delivery (Xing 2010). Phase I safety and immunogenicity study in BCG-vaccinated and nonvaccinated healthy adults is underway (ClinicalTrials.gov 2011e).

AERAS 422 (rBCG)

Aeras has developed a recombinant BCG priming vaccine currently undergoing evaluation in a phase I clinical trial in BCG-naive adults. AERAS-422 has been modified with an endosome escape mechanism and over-expresses three key TB proteins 85A, 85B and Rv3407 to elicit a greater protective immune response in the body. A second phase I trial of AERAS-422 will start later in 2011 (Leadman 2011).

Recommendations

There is overwhelming agreement that a safe, tolerable, easy-to-administer vaccine that provides lifetime protection against all forms of TB infection and disease, in all populations and age groups, will be key to reaching the goal of eliminating TB by 2050. However, few seem willing to pay for the research and development required. *The Global Plan to Stop TB 2011–2016* estimates what will be needed to develop new tools to prevent, diagnose, and treat TB.

The direct costs to develop one TB vaccine candidate for one target population could be as much as US$315 million. *The Global Plan* estimates that US$1.9 billion will be needed between 2011 and 2015 in order to have three vaccine candidates in phase III efficacy trials (Stop TB Partnership 2010). The costs of developing a new vaccine include investment in preclinical and basic science research to better understand how the immune system responds to TB and to replenish the pipeline.

Resources need to be dedicated to manufacturing the vaccine and building the capacity of clinical trial sites to conduct later-stage trials that are larger and more complex. As a vaccine trial nears regulatory approval, advocacy is needed to clarify regulatory pathways and create informed community and provider demand. Annual TB vaccine funding must reach US$250 million in 2011 and nearly US$440 million in 2015 to develop and introduce a vaccine effective against all forms of TB and for all age groups including people with and without HIV (Stop TB Partnership 2010).

Yet TB vaccine research funding—representing 18% of overall TB R&D investments—only reached US$108.8 million in 2009. The Bill and Melinda Gates Foundation is the leading funder in this research area, though its contribution declined by 40% from US$66.9 million in 2008 to US$47.6 million in 2009, and the US National Institutes of Allergies and Infectious Diseases (NIAID), the second largest funder of TB vaccine research, flatlined its contribution (Jiménez Salazar 2011). If this trend continues, it will derail progress and stall new developments. Current funders must increase their investments, and middle-income countries with high TB burdens—like Brazil, China, India, Russia, and South Africa—must commit resources to the search for a new TB vaccine.

Civil society needs to demand a better and safer TB vaccine. HIV-positive infants who are at increased risk for developing more severe forms of TB disease are unable to benefit from BCG's limited protection. Communities must participate as more than study volunteers through creating demand and advocating for their governments to invest in research and TB programs to rapidly scale up more effective vaccines. HIV treatment literacy campaigns have shown that an engaged and informed civil society is critical to accelerating research, mobilizing resources, and strengthening the national response. Advocates need to educate themselves about the gaps in TB control, understand how research can help to address them, and demand action.

Conclusion

After languishing for many years, the search for an effective TB vaccine is finally gaining momentum. With ten vaccines in clinical trials, the pipeline is the fullest it has ever been. But this progress is threatened by lack of resources and infrastructure. If these needs are not addressed, the goal of eliminating TB as a public health threat by 2050 will not be reached.

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