

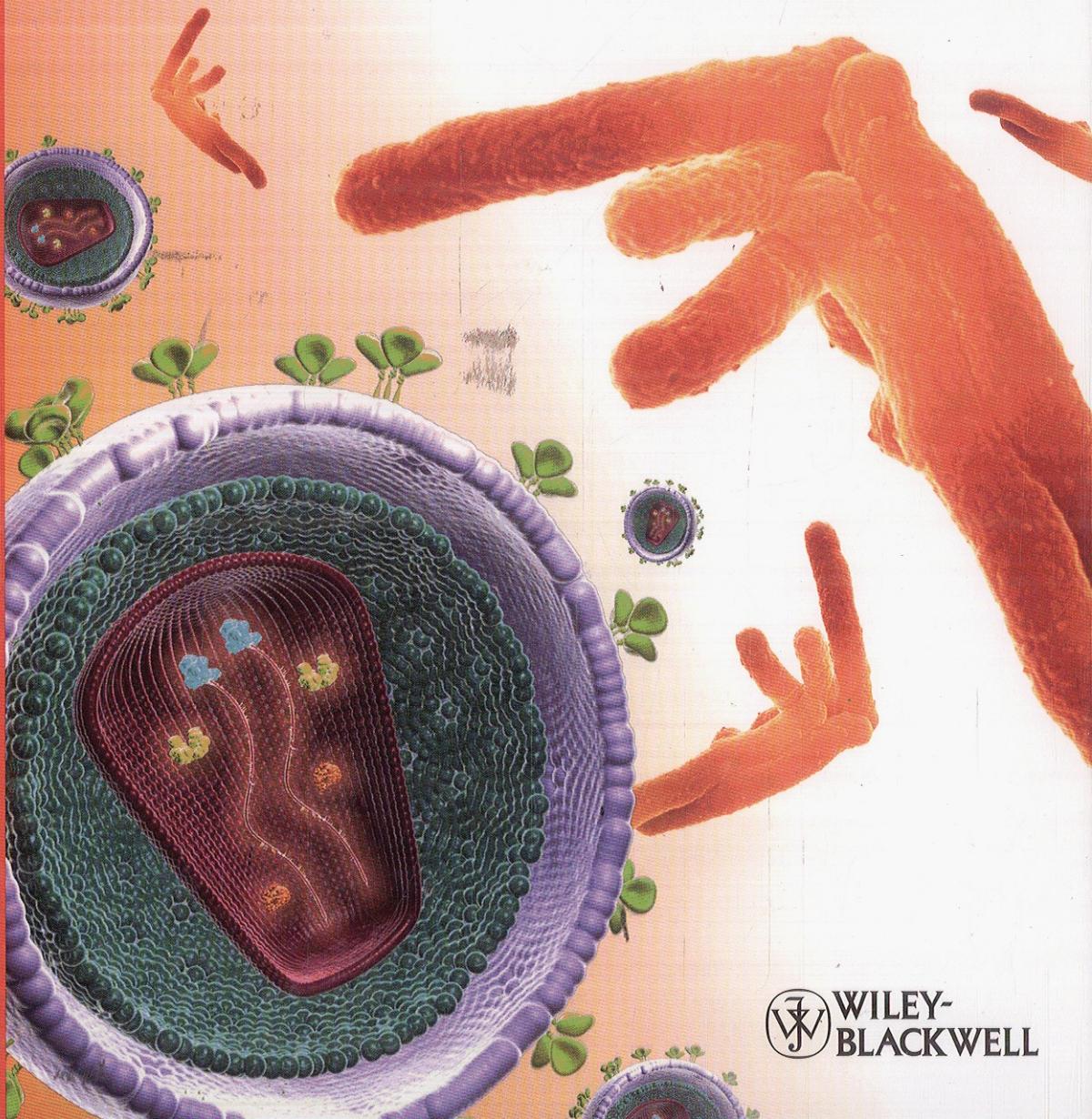


Infection Biology Handbook Series

# AIDS and Tuberculosis

A Deadly Liaison

Edited by Stefan H. E. Kaufmann  
and Bruce D. Walker



WILEY-  
BLACKWELL

# Contents

Preface XIII

List of Contributors XVII

## Part One Immunology and Vaccination Strategies for AIDS and TB 1

1	<b>HIV Immunology and Prospects for Vaccines</b>	3
	<i>Boris Jülg and Bruce D. Walker</i>	
1.1	Introduction	3
1.2	Challenges for HIV Vaccine Design	3
1.3	What Immune Responses will be Required for an Effective AIDS Vaccine?	5
1.3.1	Cytotoxic T Lymphocytes	6
1.3.2	Neutralizing Antibodies	8
1.3.3	CD4+ T Helper Cells	9
1.3.4	Natural Killer Cells	10
1.4	Models of Successful Vaccination?	10
1.5	Human Trials of AIDS Vaccines	11
1.5.1	Antibody-Based Vaccination	12
1.5.1.1	VaxGen Trial of AIDSVax	12
1.5.2	T Cell-Based Vaccination	12
1.5.2.1	The STEP Study	12
1.6	Recent Advances in Animal Models: Reasons for Optimism	13
1.6.1	Success against Heterologous Challenge	14
1.6.2	Heterologous rAd26 Prime/rAd5 Boost Vaccine Regimen	14
1.6.3	Induction of Effector Memory T-Cell Responses at Viral Entry Sites	15
1.7	The Current Vaccine Pipeline	15
1.7.1	DNA	15
1.7.2	Adenovirus	16

1.7.3	Peptides	16
1.7.4	Bacillus Calmette-Guérin	17
1.7.5	Listeria and Other Bacterial Vectors	17
1.7.5.1	<i>Listeria monocytogenes</i>	17
1.7.5.2	<i>Salmonella enterica</i>	18
1.7.5.3	Shigella	18
1.7.6	Canarypox	18
1.7.7	Adeno-Associated Virus	19
1.8	Conclusions and Future Directions	19
	References	20
<b>2</b>	<b>Immune Response to Tuberculosis as a Basis for Rational Vaccination Strategies</b>	<b>31</b>
	<i>Stefan H.E Kaufmann and Steffen Stenger</i>	
2.1	Introduction	32
2.2	Clinical Aspects of TB	32
2.3	Immune Response to TB: Innate Immunity	34
2.4	Adaptive Immunity	36
2.4.1	T-Cell Subsets	36
2.4.2	T-Cell Activation	38
2.5	Cytokines as Mediators of Immune Function	38
2.5.1	IL-12 Family of Cytokines	38
2.5.2	Tumor Necrosis Factor	40
2.6	Vaccines against TB	40
2.6.1	From the Past to the Present	40
2.6.2	The Future	42
2.6.2.1	Goals of Vaccination	42
2.6.2.2	Vaccination Strategies	44
2.6.2.3	Targets for Vaccination	46
2.7	Biomarkers	46
2.7.1	Immunologic	48
2.7.2	Transcriptomics	48
2.7.3	Proteomics	49
2.7.4	Metabolomics	49
2.8	Concluding Remarks	49
	References	50
<b>3</b>	<b>BCG Vaccination in the HIV+Newborn</b>	<b>55</b>
	<i>Willem A. Hanekom and Gregory D. Hussey</i>	
3.1	Bacillus Calmette-Guérin (BCG) and its Efficacy in Healthy Infants	55
3.2	Adverse Events Caused by BCG in Healthy Infants	56
3.3	Specific Immunity Induced by BCG in Healthy Infants	58
3.4	Efficacy of BCG to Prevent TB in HIV-Infected Infants	60
3.5	Adverse Effects Caused by BCG in HIV-Infected Infants not Receiving Antiretroviral Therapy	61

3.6	BCG Immune Reconstitution Inflammatory Syndrome (BCG-IRIS)	62
3.7	Management of BCG Disease in HIV-Infected Infants	63
3.8	Specific Immunity Induced by BCG in HIV-Infected Infants	64
3.9	Weighing up the Evidence: Should BCG be given to HIV-Infected or HIV-Exposed Infants?	65
3.10	How Can We Protect HIV-Infected Infants Against TB, if BCG is Not Given?	66
3.11	BCG Vaccination of HIV-Exposed, Uninfected Infants	67
3.12	Conclusions	69
	References	69

**Part Two Drugs 75****4 HIV/AIDS Drugs 77***Roy M. Gulick*

4.1	Introduction	77
4.2	Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs)	81
4.3	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	84
4.4	HIV Protease Inhibitors	86
4.5	Newer Classes: Entry Inhibitors and Integrase Inhibitors	90
4.5.1	Entry Inhibitors	90
4.5.2	Integrase Inhibitors	91
4.6	Newer Strategies	93
4.7	Concomitant Treatment of HIV Infection and Tuberculosis	94
4.8	Conclusions	95
	References	95

**5 *Mycobacterium tuberculosis*: Drug Resistance and Genetic Mechanisms – Facts, Artifacts, and Fallacies 103***Erik C. Böttger and Burkhard Springer*

5.1	Introduction	103
5.2	Genetic Aspects of Drug Resistance	104
5.3	Principles of Drug Susceptibility Testing in the Laboratory	108
5.4	Clinical Implications of Drug Resistance	111
5.5	Outlook and Perspectives	114
	References	115

**6 HIV-TB Drug Interactions 123***Tolu Oni, Dominique J. Pepper, and Robert J. Wilkinson*

6.1	Important Concepts and Definitions	123
6.2	Background	124
6.3	Current Therapy for TB and AIDS	124
6.4	Potential Drug–Drug and Drug–Disease Interactions	125
6.5	Treatment of Tuberculosis	126
6.5.1	Rifampin	127

6.5.2	Rifapentine	130
6.5.3	Rifabutin	130
6.5.4	Isoniazid	130
6.5.5	Pyrazinamide and Ethambutol	131
6.5.6	Ethionamide	131
6.5.7	Fluoroquinolones	131
6.5.8	Streptomycin/Amikacin/Kanamycin/Capreomycin	132
6.5.9	Terizidone/Cycloserine	132
6.5.10	Linezolid	133
6.5.11	Co-Amoxyclav	133
6.5.12	PAS	133
6.5.13	Clarithromycin	133
6.6	Treatment of HIV Infection	133
6.6.1	Fusion Inhibitors	134
6.6.2	Nucleotide/Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	134
6.6.3	Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and Protease Inhibitors (PIs)	134
6.6.3.1	Oral Bioavailability of Delavirdine and PIs	134
6.6.3.2	CYP Interactions in PIs	137
6.7	Treatment Issues in Coinfection	137
6.7.1	Shared Toxicities	137
6.7.2	TB/Antiretroviral Drug Interactions	137
6.7.2.1	Rifamycins	137
6.7.2.1.1	Rifampin + NRTI	138
6.7.2.1.2	Rifampin + NNRTI	138
6.7.2.1.3	Rifampin + PI	140
6.7.2.1.4	Rifabutin + NNRTI	141
6.7.2.1.5	Rifabutin + NRTI	141
6.7.2.1.6	Rifabutin + PI	141
6.8	Drug–Disease Interactions	141
6.8.1	TB Drugs in Development, and Potential Interactions	141
6.8.2	AIDS Drugs in Development, and Potential Interactions	142
6.8.3	Other Interactions of Note	142
6.8.3.1	Antituberculosis Drugs and Oral Hypoglycemic Agents	142
6.8.3.2	Antituberculosis Agents and Prednisolone	143
6.9	Conclusions	144
	References	144

### Part Three Clinical Issues 155

7	<b>Clinical Issues in the Diagnosis and Management of HIV Infection</b>	157
	<i>Scott Dryden-Peterson, Henry Sunpath, and Rajesh T. Gandhi</i>	
7.1	Introduction	157
7.2	Diagnosis	158
7.2.1	Rationale for Testing	158

7.2.1.1	HIV Testing for Prevention	158
7.2.1.2	Earlier Entry to Care	159
7.2.2	Recommendations for Testing	160
7.3	Methods of Testing	160
7.3.1	ELISA	162
7.3.2	Rapid Tests	163
7.3.3	Western Blot	163
7.3.4	Nucleic Acid Amplification	164
7.4	Management of the Newly Diagnosed HIV-Infected Patient	164
7.4.1	Assessment of Baseline HIV Parameters	164
7.4.2	Concurrent Infection	165
7.4.2.1	Tuberculosis	165
7.4.2.2	Sexually Transmitted Infections	167
7.4.2.3	Viral Hepatitis	167
7.4.2.4	Other Infections	168
7.4.3	Comorbid Conditions	170
7.4.4	Adherence Assessment	170
7.4.5	Prophylaxis	171
7.5	Antiretroviral Therapy	171
7.5.1	When to Start	171
7.5.1.1	Asymptomatic Patients	171
7.5.1.2	Patients with Tuberculosis	172
7.5.1.3	Patients with an Opportunistic Infection	173
7.5.1.4	Primary HIV Infection	173
7.5.2	Choice of Initial Therapy	174
7.5.2.1	Backbone: Nucleoside Reverse Transcriptase Inhibitors	174
7.5.2.2	Anchor: Non-Nucleoside Reverse Transcriptase Inhibitors or Protease Inhibitors	177
7.5.3	Monitoring	178
7.6	Summary and Conclusions	179
	References	180

8	<b>HIV-Associated Tuberculosis: Clinical Challenges</b>	191
	<i>Neil W. Schluger</i>	
8.1	Introduction	191
8.2	Epidemiology of Tuberculosis in HIV-Infected Persons	191
8.3	Clinical Issues in the Care of HIV-Infected Patients with Tuberculosis	192
8.3.1	Latent Tuberculosis Infection (LTBI)	192
8.3.1.1	LTBI Diagnosis	193
8.3.1.1.1	The Tuberculin Skin Test	193
8.3.1.1.2	The Interferon-Gamma Release Assay	194
8.3.1.2	LTBI Treatment	195
8.3.1.2.1	Two-Month Regimens	195
8.3.1.2.2	Three-Month Regimens	195

8.3.1.2.3	Four-Month Regimens	195
8.3.1.2.4	Isoniazid	196
8.3.2	Active Tuberculosis	196
8.3.2.1	Active Tuberculosis Diagnosis	196
8.3.2.1.1	Clinical Presentation	196
8.3.2.1.2	Chest Radiography	197
8.3.2.1.3	Sputum Smear and Culture	197
8.3.2.2	Active Tuberculosis Treatment	198
8.3.2.2.1	The Drug Regimen	198
8.3.2.2.2	Drug Combinations and Interactions	199
8.3.2.2.3	Dosing Frequency	201
8.3.2.2.4	Duration of Therapy	201
8.3.2.2.5	Immune Reconstitution Inflammatory Syndrome (IRIS)	202
8.4	Conclusions	203
	References	203

## 9 TB/AIDS Coinfection: An Integrated Clinical and Research Response 209

*Anne E. Goldfeld and Elizabeth L. Corbett*

9.1	Introduction	209
9.2	TB/HIV Epidemiology	215
9.2.1	Global Epidemiology of HIV/TB Coinfection and Disease: Estimates and Regional Time Trends	215
9.2.1.1	Trends in the Global HIV/TB Epidemic Since 2000	216
9.2.1.1.1	The Example of Sub-Saharan Africa	216
9.2.1.1.2	HIV/TB Incidence in Other Global Regions	218
9.2.2	HIV as a Risk Factor for TB in the Pre- and Post-ART Era	218
9.2.3	The Secondary Impact of HIV-Related TB on Global TB Transmission Rates and Population Genetics of <i>M. tuberculosis</i>	219
9.2.3.1	HIV and TB Transmission Rates at the Community Level	220
9.2.3.2	HIV and Institutional TB Transmission	222
9.2.3.3	HIV and TB Population Genetics and the Coinfected Individual	223
9.2.4	The Impact of Pathogen and Host Genetics on Disease Outcome in TB/HIV Coinfection	223
9.2.4.1	The Impact of HIV Subtype Specificity on HIV Regulation and Disease Outcome in TB/HIV Coinfection	224
9.2.4.2	The Impact of TB Strain Variability on HIV Regulation and Disease Outcome in TB/HIV Coinfection	225
9.2.4.3	The Impact of Host Variability and Disease Outcome on TB/HIV Coinfection	225
9.3	Clinical Aspects of TB Disease in the HIV-Infected Patient	226
9.3.1	Chronic Cough and other Common Clinical Presentations of HIV/TB	227
9.3.2	Diagnosis of HIV-Related TB Infection and Disease	229

9.3.3	Excluding TB in the Context of HIV Care	229
9.3.4	Treatment of Latent TB, and Preventive Therapy	230
9.4	Treatment of HIV-Infected TB Patients	231
9.4.1	Reducing Mortality in HIV-Infected TB Patients	232
9.4.2	Antituberculosis Regimens	232
9.4.3	Choice of Antiretrovirals in the Context of Treating TB	233
9.4.4	When to Start ART?	234
9.4.5	Immune Reconstitution in TB/HIV Coinfection	235
9.5	Critical Issues in the Delivery of Coordinated TB and HIV Prevention and Care	239
9.5.1	An Example of Linking TB and HIV/AIDS Care at the Community Level	239
9.6	Conclusions	241
	References	242
<b>10</b>	<b>Extensively Drug-Resistant Tuberculosis and HIV/AIDS</b>	<b>253</b>
	<i>Megan Murray and Ted Cohen</i>	
10.1	Introduction	253
10.2	The Burden of XDR TB and HIV	254
10.3	Evidence of a Causal Association Between HIV and Drug-Resistant TB	255
10.4	Mechanisms by which HIV may Lead to Drug Resistance in TB	255
10.4.1	Acquired Resistance	257
10.4.2	Primary Resistance	259
10.5	Role of HIV on the Infectiousness of XDR TB	261
10.6	Community Level Impact of HIV on Population Increases in Drug-Resistant TB	262
10.7	Effect of HIV on the Diagnosis and Treatment of MDR and XDR TB	262
10.7.1	Diagnosis	262
10.7.2	Treatment	263
10.8	Future Directions	267
	References	267
<b>11</b>	<b>Clinical Issues (Including Diagnosis): Immune Reconstitution Inflammatory Syndrome (IRIS)</b>	<b>277</b>
	<i>Martin P. Grobusch, Colin N. Menezes, and Melanie-Anne John</i>	
11.1	The Problem of IRIS: An Overview	277
11.1.1	Introduction	277
11.1.2	Pathogenesis	278
11.1.3	Defining IRIS	280
11.2	Tuberculosis-Related IRIS	280
11.2.1	Case Definitions and Diagnostic Criteria	280
11.2.2	Epidemiology	281

11.2.3 Clinical Manifestations 283

11.2.4 Management 284

11.2.5 Prevention 285

References 286

**Index 291**